CHARLES UNIVERSITY

Faculty of Science

Study programme: Clinical and Toxicological Analysis

Gabriela Presová

OXIDATIVE CYCLIZATIONS OF ENOLATES FOR SYNTHESES OF NATURAL STILBENOLIGNANS

Oxidativní cyklizace enolátů pro syntézy přírodních stilbenolignanů

Bachelor thesis

Supervisor: Dr. habil. Ullrich Jahn, Ph.D.

Consultant: Ing. Tomáš Mašek

Prague 2018

Prohlášení

Prohlašuji, že jsem tuto závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Dále prohlašuji, že tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

Jsem si vědoma toho, že případné využití výsledků, získaných v této práci, mimo Univerzitu Karlovu, je možné pouze po písemném souhlasu této univerzity.

Tato bakalářská práce byla vypracována na Ústavu organické chemie a biochemie AV ČR, v. v. i..

V Praze, dne 18. 5. 2018 ……..……

Gabriela Presová

Acknowledgement

I would like to thank my supervisor Dr. habil. Ullrich Jahn for the supervision and the opportunity to work without any experiences in his research group and for the advices which always moved me further.

At second, I would like to thank my consultant Ing. Tomáš Mašek for introducing me synthetic organic chemistry, laboratory techniques and this interesting project. He explained me everything with patience and always tried to help me find solution in difficult situations.

In this way, I would also like to thank my colleagues from the research group Jakub Smrček, Anna Hlaváčková, Tereza Pavlíčková, Chiranan Pramthaisog, Aurelia Maria Bosi, Trong Phan Nguyen Huu, Michal Šimek, David Just, Václav Chmela, Denisa Hidasová, Adrián Kocian, Mikhail Klychnikov, Victor Golubev, Emanuela Jahn, Pratap Jagtap, Shraddha Mahamulkar, Ameneh Tatar and Irena Dokli for practical or theoretical advices and friendly working environment.

Special thank belongs to Dr. Radek Pohl for NOE experiments and Dr. Ivana Císařová for X-ray crystallographic analyses of my samples.

The biggest thank belongs to my boyfriend Petr Štěpančík and family particularly my parents and siblings for the support, patience, inspiration and motivation during studying and for their love and belief in me, which always makes me stronger.

Abstract

In this thesis, the development of a new tandem method and its application to the synthesis of stilbenolignan analogues containing arylindane motif is reported. The tandem process includes the nucleophilic conjugate addition followed by the oxidative radical cyclization, where the generated 1,4-adduct is oxidized by a ferrocenium salt, cyclizes in 5-exo-trig mode and subsequently lactonizes. The resulting product contains an arylindane unit linked to a tetrahydrofuranone, therefore this method represents a synthetic approach to the main skeleton of arylindane stilbenolignans. The use of differently methoxylated starting materials led to synthesis of compounds structurally and configuratively approaching the natural stilbenolignans with interesting biological activity.

Abstrakt

V této práci je popsán vývoj nové tandemové metody s jejím využitím pro syntézu stilbenolignanových analogů obsahujících aryl-indanový motiv. Tento tandemový proces zahrnuje nukleofilní konjugovanou adici následovanou oxidativní radikálovou cyklizací, kde generovaný 1,4-adukt je oxidovaný ferroceniovou solí, cyklizuje v režimu 5-exo a následně laktonizuje. Výsledný produkt obsahuje arylindanovou jednotku spojenou s tetrahydrofuranonem, proto tato metoda představuje syntetický přístup k základnímu skeletu arylindanových stilbenolignanů. Použití různě methoxylovaných výchozích látek vedlo k syntéze produktů přibližujících se svou strukturou a konfiguracím přírodním stilbenolignanům se zajímavou biologickou aktivitou.

List of abbreviations and symbols

4CL	4-coumarate:CoA ligase
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
APT	Attached proton test
ATR	Attenuated total reflectance
Bu	Butyl
C3H	*p*-Coumarate 3-hydroxylase
C4H	Cinnamate 4-hydroxylase
CAD	Cinnamyl alcohol dehydrogenase
CCR	Cinnamoyl-CoA reductase
CL	Coumarate:CoA ligase
COMT	Caffeate o-methylfransferase
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
DCM	Dichloromethane
DIPA	Diisopropylamine
DME	Dimethoxyethane
DPPH	2,2-diphenyl-1-picrylhydrazyl
EA	Ethyl acetate
EI	Electron ionization
ESI	Electrospray ionization
Et	Ethyl
FCR	Functional Capability Requirement
HMBC	Heteronuclear multiple bond correlation
HMPA	Hexamethylphosphoramide
HSQC	Heteronuclear single-quantum correlation
INDOR	Internuclear double resonance
IR	Infrared
Me	Methyl

MS	Mass spectrometry
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
Nu	Nucleophile
PAL	Phenylalanine ammonia lyase
r.t.	Room temperature
SET	Single electron transfer
STS	Stilbene synthase
THF	Tetrahydrofurane
TMEDA	Tetramethylethylenediamine
TNF	Tumor necrosis factor
UV	Ultraviolet

Table of Contents

1 INTRODUCTION

Stilbenolignans are polyphenolic secondary metabolites of plants belonging to a group termed "non-conventional lignans", which also include coumarinolignans or flavonolignans. Stilbenolignans have a phenylpropyl unit as all lignans, but additionally these compounds contain a stilbene unit that places them also under the category of stilbenes (**Figure 1.1**).[1] For better understanding to these natural compounds, the terms stilbene and lignan are defined in following paragraphs.

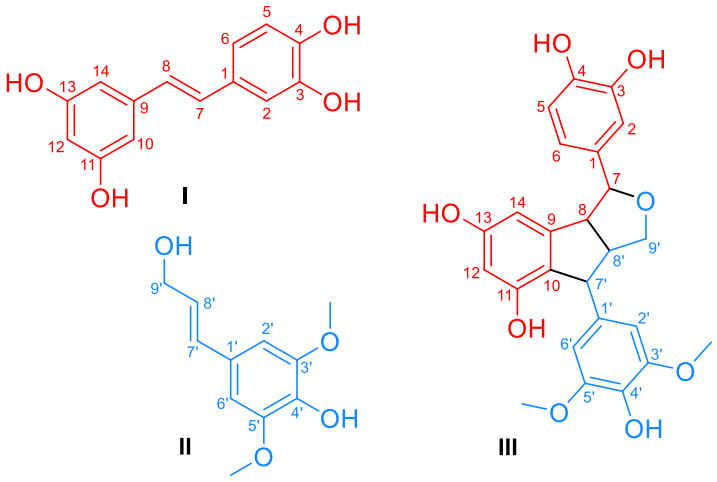


Figure 1.1 Examples of the stilbene piceatannol (**I**) and monolignol sinapyl alcohol (**II**) as structural subunits of the stilbenolignan kompasinol A (**III**) with numbering system based on biosynthesis.

Stilbenes are characterized by the 1,2-diphenylethylene backbone. They are one of the most studied natural products for their biological activities and possible pharmacological applications. Some of them are antimicrobial compounds classified as phytoalexins or they are biosynthesized for signalling of defence responses, protection against UV light damage, and increase in bioavailability of recalcitrant nutrients.[2–5] Stilbenoids are the most common subclass of stilbenes as their hydroxylated derivatives, which are derived from the basic unit 3,5,4'-trihydroxy-*trans*-stilbene called resveratrol (**IV**).[2] Resveratrol-based oligomers including oxyresveratrol (**V**), isorhapontigenin (**VI**), piceatannol (**I**) and its oligomers have similar significant activity profiles to resveratrol (**Figure 1.2**, p. 9) and are also known members of stilbenoids.[6–10]

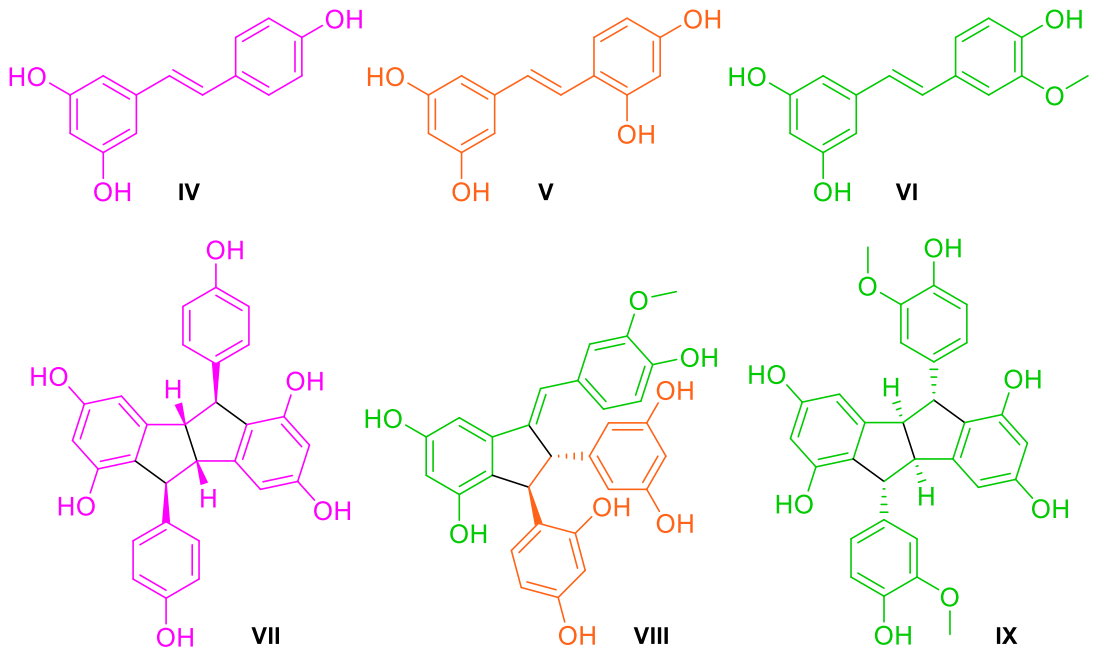


Figure 1.2 Examples of stilbenoid dimers – pallidol (**VII**), gnetuhainin J (**VIII**) and gneafricanin F (**IX**) with corresponding monomers **IV**-**VI**.

Lignans are natural products composed of a dimeric structure formed by linking two phenylpropanoid units (monolignols).[1] Lignans represent a class of pharmacologically active substances exhibiting antioxidant, antitumor, anti-inflammatory and anti-viral properties.[11] The linkage between two phenylpropene units may have a variable degree of oxidation in the side-chain and the aromatic moieties are substituted by different patterns.[12] Lignans are divided into two main subclasses according to type of linkage. When phenylpropane units are linked by bond between positions C-8 and C-8', the compounds are simply named as "lignans". "Neolignans" are compounds which have units linked differently or contain ether oxygen in the linkage.[1] Moreover, the subclass of lignans is divided into eight groups and neolignans are classified into fifteen groups.[12] For example, arylindane lignans belonging to neolignan family are formed by dimerization of arylpropenes (**Figure 1.3**, p. 10).[13] The main feature of arylindane lignan skeleton is also present in some types of stilbenolignans.

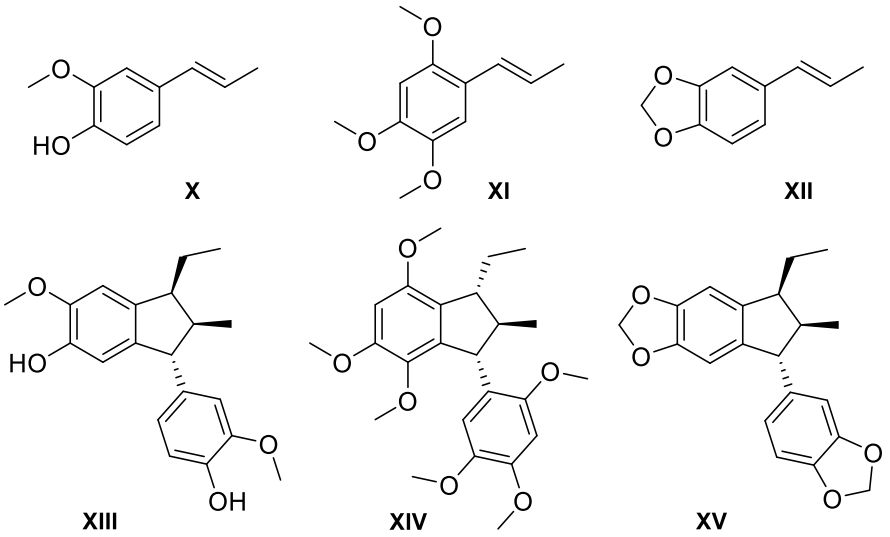


Figure 1.3 Members of arylindane lignans – diisoeugenol (**XIII**), diasarone (**XIV**), diisosafrole (**XV**) with monomers - isoeugenol (**X**), asarone (**XI**), isosafrole (**XII**).

Most of stilbenolignans have significant biological properties, they have been proven as anti-inflammatory compounds and potent anti-oxidants.[1,14] Some of them are inhibitors of cyclooxygenase-1 and -2,[15] inhibitors of blood vessel growth and anti-angiogenic compounds,[16] inhibitors of TNF-α production,[14] or inhibitors of α-glucosidase.[17]

In various publications, different numbering systems for stilbenolignans are used. The most common system is based on the biogenesis and it starts from the aromatic ring of the monolignol unit[1] (**Figure 1.1**, p. 8). For this thesis, a unified numbering system based on the method of synthesis will be used, which is shown in **Figure 1.4**.

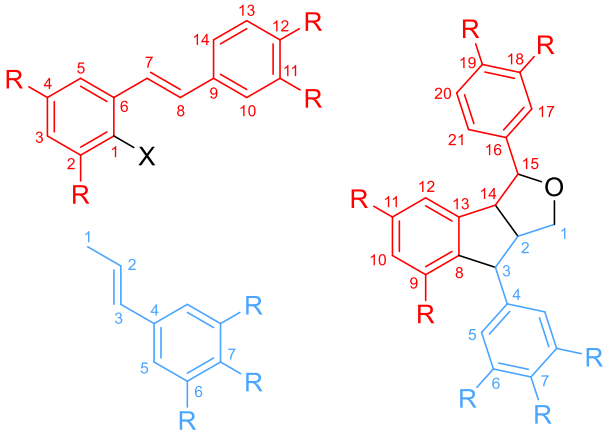
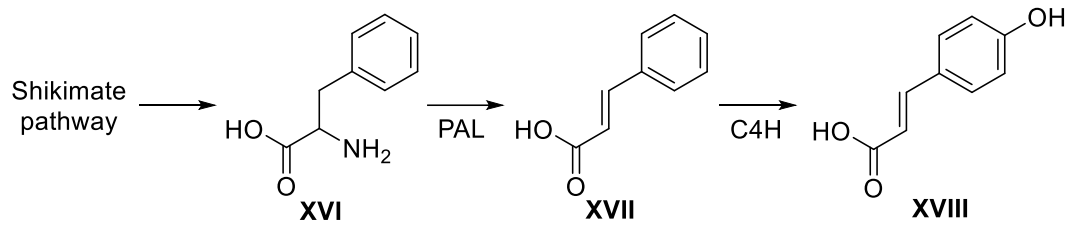


Figure 1.4 Numbering system for stilbenolignan derivatives used in this thesis.

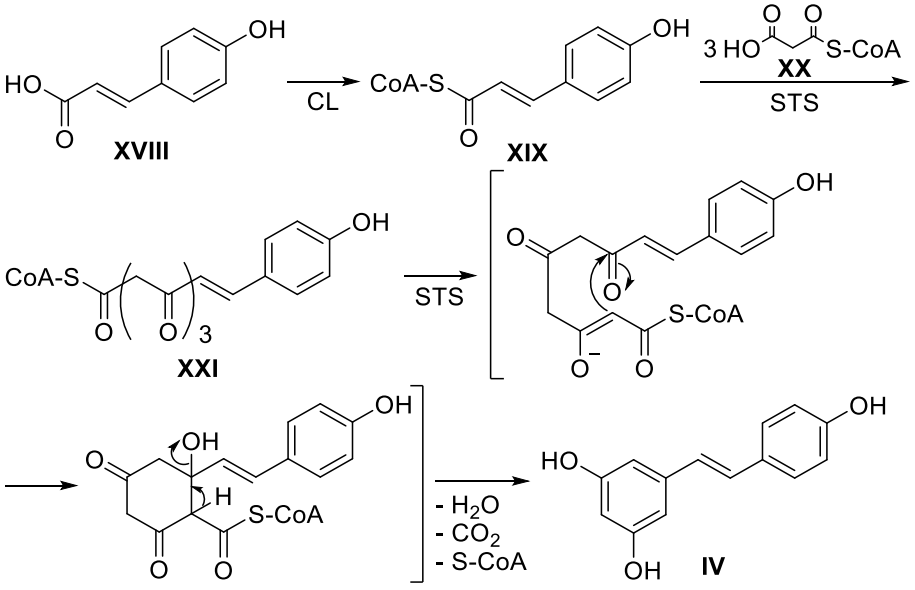
1.1 Biogenesis of stilbenolignans

Plant stilbenes and lignans are derived from the general phenylpropanoid pathway. The biosynthesis of phenylpropanoids starts with the amino acid phenylalanine (**XVI**), which is the product of the shikimate pathway.[12,18] The first reaction of the phenylpropanoid pathway produces cinnamic acid (**XVII**), which is the collective intermediate for all phenylpropanoids.[19,20] Often this is followed by cinnamate hydroxylase catalyzed hydroxylation leading to coumaric acid (**XVIII**) (**Scheme 1.1**).[21]



Scheme 1.1 Early steps of phenylpropanoid pathway. PAL = phenylalanine ammonia lyase and C4H = cinnamate 4-hydroxylase.

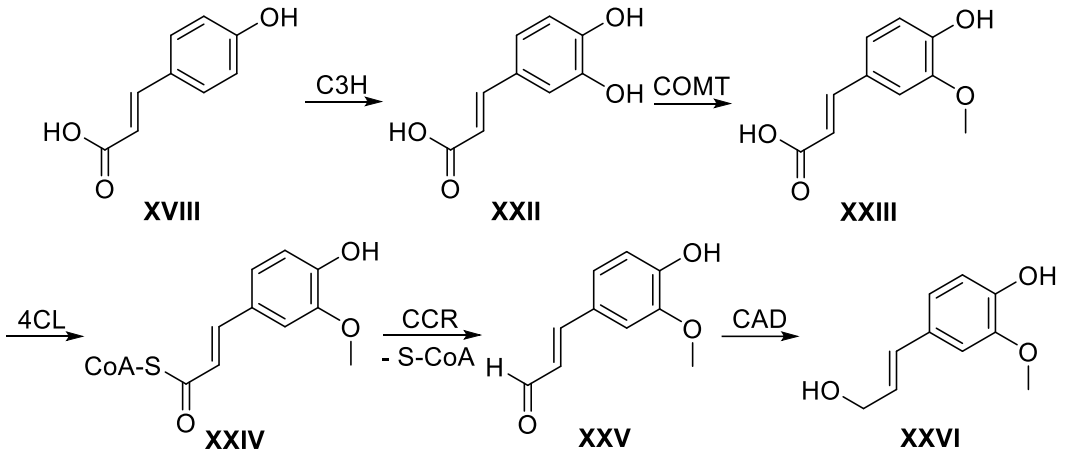
After activation as coumaroyl-CoA (**XIX**) a tetraketide intermediate (**XXI**) is formed by a reaction with three molecules of malonyl-CoA (**XX**), which is catalyzed by stilbene synthase.[22] The same enzyme subsequently catalyzes an intramolecular aldol condensation, accompanied by decarboxylation and dehydration (**Scheme 1.2**).[23]



Scheme 1.2 Biosynthetic pathway of stilbenes. CL = coumarate:CoA ligase, STS = stilbene synthase.

These steps catalyzed by stilbene synthase are characteristic only for stilbenes and therefore stilbene synthase is a key enzyme of its biosynthesis. The final product of this pathway is resveratrol (**IV**). All higher plants seem to be able to synthesize cinnamic acid derivatives, but only a few plant species produce stilbenes.[2]

In the case of lignan biosynthesis, characteristic steps follow formation of coumaric acid (**XVIII**), which can be hydroxylated and subsequently methylated to produce caffeic acid (**XXII**) and ferulic acid (**XXIII**). Subsequently, ferulic acid is activated by 4-coumarate:CoA ligase, which leads to the formation of feruloyl-CoA (**XXIV**). In the following step, cinnamoyl-CoA reductase catalyzes reduction of the ester to the corresponding aldehyde with elimination of coenzyme A. Another reduction of coniferaldehyde (**XXV**) to coniferyl alcohol (**XXVI**) is catalyzed by cinnamyl alcohol dehydrogenase.[24] The resulting alcohol is a key structure in this biosynthetic pathway (**Scheme 1.3**), because is the precursor of most lignans.[12] Different types of lignans are formed by subsequent oxidative coupling of two alcohol units.[1]

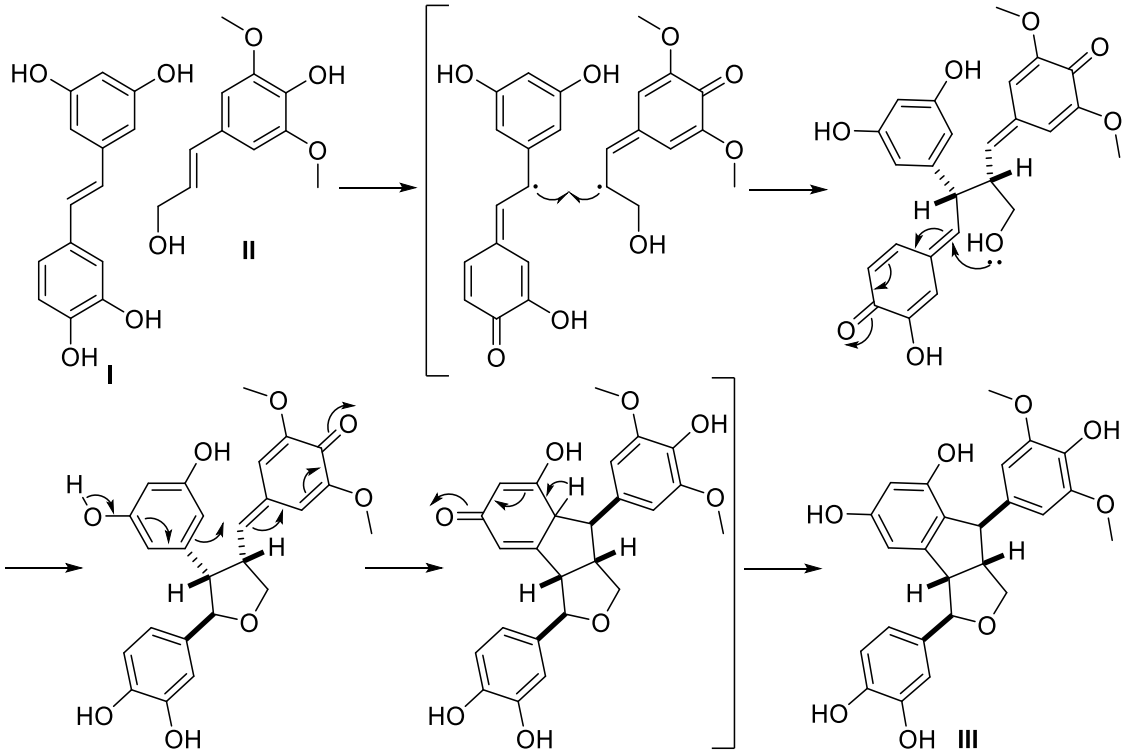


Scheme 1.3 Early steps of lignan biosynthesis. C3H = *p*-coumarate 3-hydroxylase, COMT = caffeate *o*-methyltransferase, 4CL = 4-coumarate:CoA ligase, CCR = cinnamoyl-CoA reductase and CAD = cinnamyl alcohol dehydrogenase.

Glycosylation, methoxylation, oligomerization, isomerization or prenylation are common post-synthetic modification of stilbenes as well as lignans.[12,22]

The linkage between stilbenes and lignans is probably formed through oxidative radical coupling. For example, during the biogenesis of kompasinol A (**III**), a piceatannol (**I**) derived radical couples with a radical derived from sinapyl alcohol (**II**). The resulting *p*-quinone methide intermediate cyclizes to form the dihydrofuran

bridge, followed by the Michael-type cyclization to the final product (**Scheme 1.4**). This reaction could be enzymatic or non-enzymatic, because literature has shown isolation of stilbenolignans as racemates and in fewer cases as pure enantiomers.



Scheme 1.4 Biogenesis proposal for kompasinol A (**III**). Relative configuration of structures was based on published relative configuration of **III**.

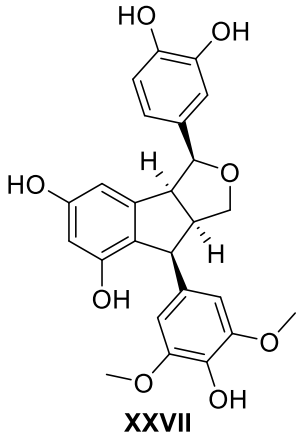
1.2 Stilbenolignans containing arylindane motif

Cararosin A (**XXVII**), gnetifolin F (**XXVIII**), lehmbachol D (**XXIX**) and kompasinol A (**III**) are produced by plants from different families, but these compounds contain the same skeleton feature composed of the arylindane unit linked to a tetrahydrofuran unit and two extra aromatic rings. All of them are thus members of arylindane lignans and stilbenolignans.

1.2.1 Cararosin A

In 2003, cararosin A (**XXVII**) was firstly isolated from the small shrub *Caragana rosea* Turcz. (Leguminosae).[25] This compound was also obtained from the red heartwood of *Caragana changduensis* in 2017.[26] Both plants grow in the north and east of China and have been used as a folk medicine for their antioxidant, anti-viral and

anti-inflammatory activity.[27,28] Moreover, *C. rosea* showed anti-HIV activity in preliminary screening of Traditional Chinese Medicine.[27] According to this result, compound **XXVII** isolated as single enantiomer was tested, but did not show any promising activity of anti-HIV *in vitro*. The structure of **XXVII** has been established by the spectroscopic data (**Figure 1.5**), but the absolute stereochemistry remains unknown.[25]



XXVII

Figure 1.5 Relative configuration of cararosin A.

1.2.2 Gnetifolin F and lehmbachol D

Gnetifolin F (**XXVIII**) was initially isolated from the lianas of *Gnetum parvifolium* (Gnetaceae) in 1991.[29] This plant grows in the south of China and has been used in the treatment of bronchitis and arthritis with some other Gnetum species in folk medicine.[30] The structure of this compound and its acetylated derivative was determined mostly by NMR and MS spectroscopy. Gnetifolin F (**XXVIII**) was also extracted from *Gnetum klossii* (Gnetaceae) in 2003.[31] In both cases, the relative stereochemistry of this compound has been determined by NOE analysis, but the configuration of the two aryls has been assigned differently in each case, as shown in **Figure 1.6** (p. 15).

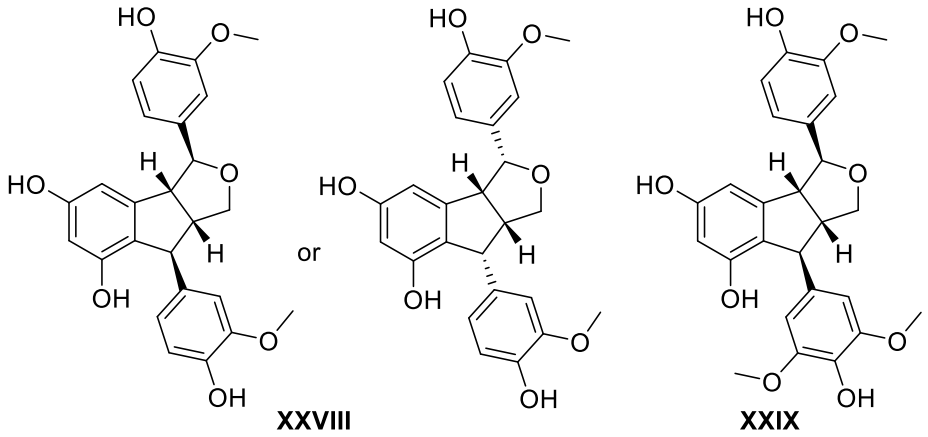


Figure 1.6 Relative configurantion of gnetifolin F (**XXVIII**) and lehmbachol D (**XXIX**).

Lehmbachol D (**XXIX**) was isolated as single diastereomer from the bark of *Salacia lehmbachii* (Celastraceae) from Papua New Guinea in 1997.[32] The structure of this compound was assigned by NMR, MS and IR spectra. The relative configuration of **XXIX** has been determined by NOE experiment in 2006 (**Figure 1.6**), when this substance was isolated together with gnetifolin F (**XXVIII**) from *Gnetum cleistostachyum* (Gnetaceae).[14]

Gnetifolin F (**XXVIII**) with lehmbachol D (**XXIX**) have been pharmacologically tested and anti-inflammatory activity have been proved, because these substances inhibit TNF-α production by murine peritoneal macrophages.[14]

1.2.3 Kompasinol A

Kompasinol A (**III**) was first isolated from the heartwood of *Maackia amurensis* (Fabaceae) as maackoline in 1995. This palm grows in the south of the Russian Far East, in the Mandshuria and Korea[33]. Kompasinol A (**III**) obtained its more common name in the following year, when it was isolated from the bark of *Koompassia malaccensis* (Fabaceae), a large tree occurring in southern Thailand, Malaysia, and on Sumatra and Borneo.[34] Both names kompasinol A and maackoline are used in the literature, however only kompasinol A will be used in this thesis.

The structures of **III** and its pentamethylated and pentaacetylated derivatives were determined by spectral data and NOE experiments suggested a relative configuration (**Figure 1.7**, p. 16). The spectral data of **III** and **XXVIII** show similarity, which may indicate the same relative configuration of these compounds.[29,33,34]

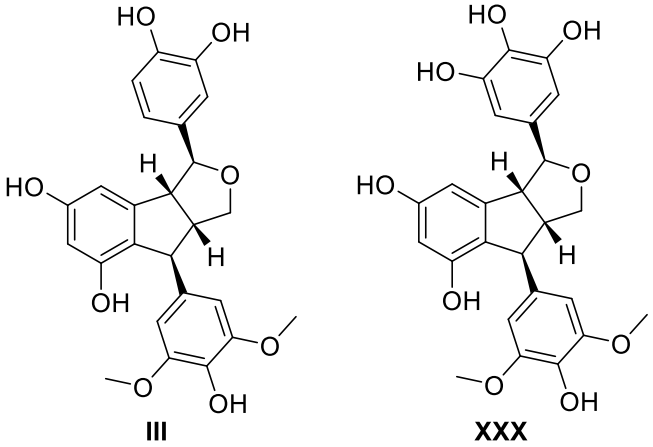


Figure 1.7 Relative configuration of kompasinol A (**III**) and kompasinol B (**XXX**).

In the following years, kompasinol A (**III**) was also extracted from the stems of *Caragana tibetica* (Fabaceae)[35] in 2005, the seeds of *Syagrus romanzoffiana* (Arecaceae)[17], the tubers of *Smilax china* (Smilacaceae)[36] in 2008 and the rhizomes of *Smilax glabra* (Smilacaceae)[37] in 2013.

Each of mentioned plants containing **III** have medical value for its antioxidant properties,[37,38] antimicrobial activity,[39] or they are used for the treatment of toxic damage of the liver,[37,40] dysentery,[34] hypertension and arthritis.[35] However, in many cases the biological activity was showed by complex of polyphenolic compounds in the extract and not by kompasinol A (**III**) itself.

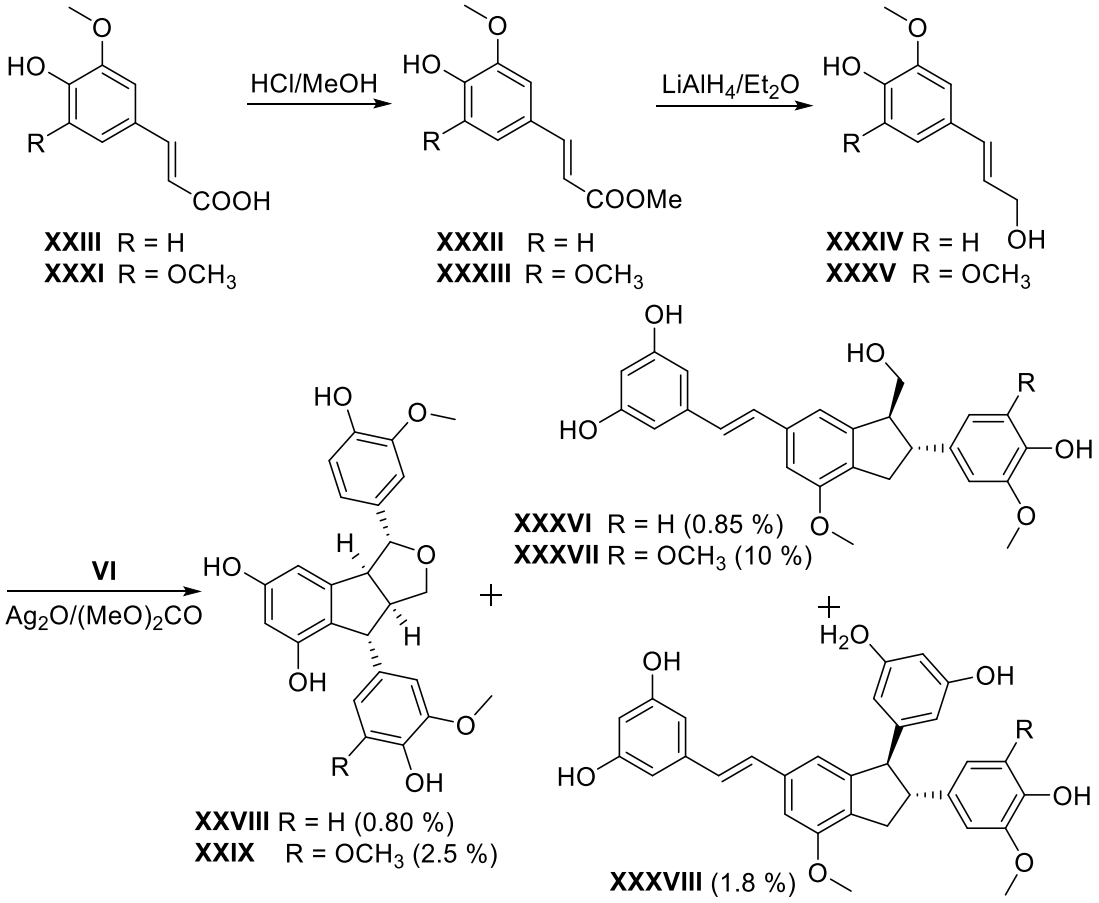
The antioxidant activity of **III** has been proved in two cases. In 2005, when **III** was isolated from the stems of *Caragana tibetica* and the scavenging activity of superoxide anion was tested.[35] In 2012, kompasinol A (**III**) isolated from *Maackia amurensis* was tested by the DPPH method for the determination of antioxidant activity, the ABTS method for antiradical activity, the FCR method for reducing capability and the inhibition effect of initiated oxidation of linoleic acid.[38] In both cases, the assays showed significant antioxidant activity of **III**.

Moreover, another type of biological activity has been proved for kompasinol A (**III**) and its hydroxylated derivative kompasinol B (**XXX**) (**Figure 1.7**) isolated from the *Syagrus romanzoffiana*. Both possess inhibitory activity against α-glucosidase type IV from Bacillus Stearothemophilus. According to the rat model bioassay, kompasinol A (**III**) has significant effect in reducing the postprandial blood glucose level, which indicate its therapeutic potential as hypoglycemic agent.[17]

1.3 Known synthetic approaches to arylindane skeleton

A synthetic approach to arylindane basic skeleton is proposed in a few publications.[13,41–45] The synthesis of arylindane stilbenolignans is the topic of only three articles.[14,46]

The only known synthetic approach to gnetifolin F (**XXVIII**) and lehmbachol D (**XXIX**) inspired by biogenetic pathway was published in 2006 (**Scheme 1.5**).[14]



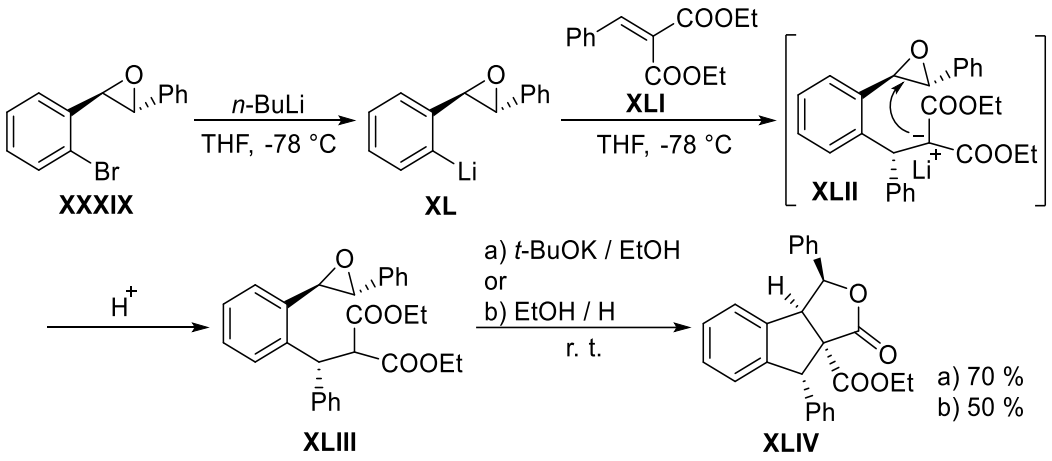
Scheme 1.5 Synthetic route of gnetifolin F (**XXVIII**), lehmbachol D (**XXIX**), gnetucleistol F (**XXXVI**), gnetofuran A (**XXXVII**) and shegansu B (**XXXVIII**).

Ferulic acid (**XXIII**) or sinapic acid (**XXXI**) and isorhapontigenin (**VI**) were used as the starting materials in this biomimetic synthesis. In the first step, ferulic acid or sinapic acid were esterified to obtain the methyl esters **XXXII** or **XXXIII**, which were converted to phenylpropenols **XXXIV** or **XXXV** by reduction with lithium aluminium hydride. Oxidative coupling reactions of the phenylpropanols and isorhapontigenin (**VI**) mediated by silver(I) oxide in dimethyl carbonate yielded a mixture of gnetifolin F (**XXVIII**), lehmbachol D (**XXIX**) together with gnetucleistol F (**XXXVI**),

gnetofuran A (**XXXVII**) and shegansu B (**XXXVIII**).[14] In the case of lehmbachol D (**XXIX**), the relative configuration was established by NOE experiments. The relative stereochemistry of the other products **XXVIII**, **XXXVI**, **XXXVII** and **XXXVIII** was assigned based on comparison of physical and spectroscopic data with those of the compound obtained by Lin *et al*.

In 2008, a biomimetic preparation of oligostilbenes including kompasinol B (**XXX**) and its analogues was published. The synthesis was based on oxidative coupling of resveratrol and ethyl methoxycinnamate by hydrogen peroxide in the presence of horse radish hydrogen peroxide and subsequent aromatic electrophilic substitution which led to **XXX**.[47]

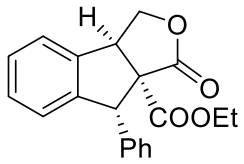
Another synthetic approach to arylindane stilbenolignans was published in 2008, when a tri- and disubstituted tetrahydroindenofuranone derivatives was synthesized. Although the original aim of that synthesis was a structural analogue of epipodophyllotoxin, a compound containing the structural skeleton of arylindane stilbenolignans was also obtained. The approach to this tetrahydroindenofuranone derivative was based on the Michael addition of *o*-lithiated aryloxiranes to a benzylidene malonate, followed by nucleophilic oxirane ring-opening and subsequent lactonization (**Scheme 1.6**).[46]



Scheme 1.6 Synthesis of tetrahydroindenofuranone **XLIV**.

The first step of the reaction was lithium-bromide exchange, when *o*-bromostilbene oxide (**XXXIX**) reacted with *n*-butyl lithium to generate *ortho*-lithiated *trans*-1,2-disubstituted oxirane (**XL**), which reacted with benzylidenemalonate (**XLI**). This Michael addition generated the 1,4-adduct **XLIII** as a single diastereomer

via intermediate **XLII**, which then cyclized on the oxirane ring via a stereospecific intramolecular 5-exo cyclization and successive lactonization forming the tetrahydroindenofuranone (**XLIV**) as the sole diastereomer. The relative configuration of the product does not correspond to the relative configuration of the natural compounds and was determined by analogy of the NMR data with a reference homolog **XLV**. The relative configuration of the reference product was proposed only by consideration of coupling constant values of the ^{1}H NMR spectra (**Figure 1.8**) .[46]



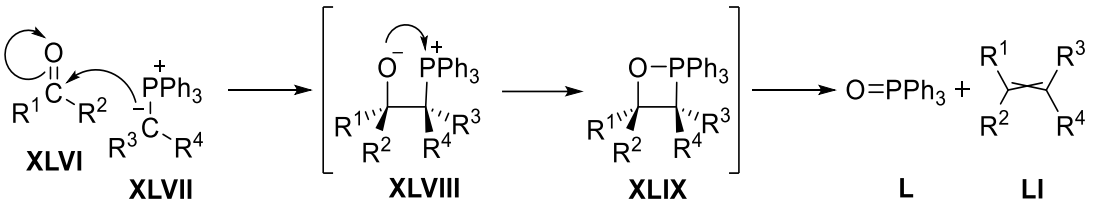
XLV

Figure 1.8 Relative configuration of reference compound **XLV**.

1.4 Potential synthetic approach to the stilbenolignans containing arylindane motif

The development of the a new synthetic method was motivated by the prospect of confirming the stereostructure of arylindane stilbenolignans and investigating their biological activity. Moreover, the biological activity of these compounds was tested on racemic mixtures of enantiomers with each probably having different biological activity. Separation of these racemates would be difficult. Therefore, a potential enantioselective synthesis in order to determine the activity of individual enantiomers is another motivation.

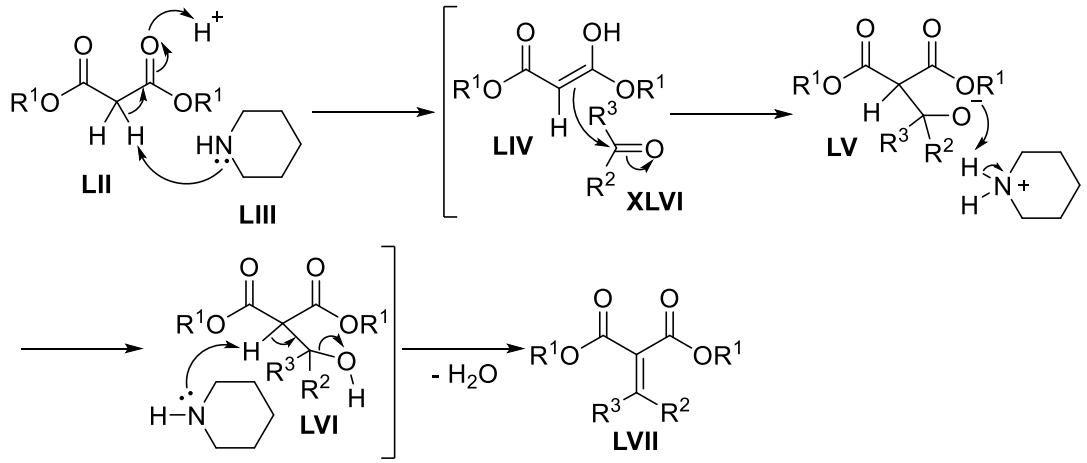
The Wittig or Wittig-Horner reactions can be used for the synthesis of stilbenes. These reactions allow the preparation of alkenes by reaction of an aldehyde or ketone (**XLVI**) with a phosphonium ylide (**XLVII**). The ylide **XLVII** can be easily generated by an S_N2 reaction of alkyl halides with triphenylphosphine and following reaction with a base. In the Wittig reaction, the first step may be procced by addition of the ylide **XLVII** to the carbonyl group to form cyclic intermediate oxaphosphetane (**XLIX**) or by the initial generation of dipolar intermediate betaine (**XLVIII**), which subsequently cyclizes to oxaphosphetane (**XLIX**) (**Scheme 1.7**, p. 20).[48]



Scheme 1.7 Mechanism of the Wittig reaction.

The driving force in the second step is formation of a very stable phosphine oxide (**L**) accompanied by formation of the *E/Z* stereoisomers of the alkene (**LI**). The Wittig-Horner reaction mechanism is very similar, but aldehydes or ketones react with a phosphonate carbanion. In this case the reaction leads to alkenes with *E*-selectivity.[49]

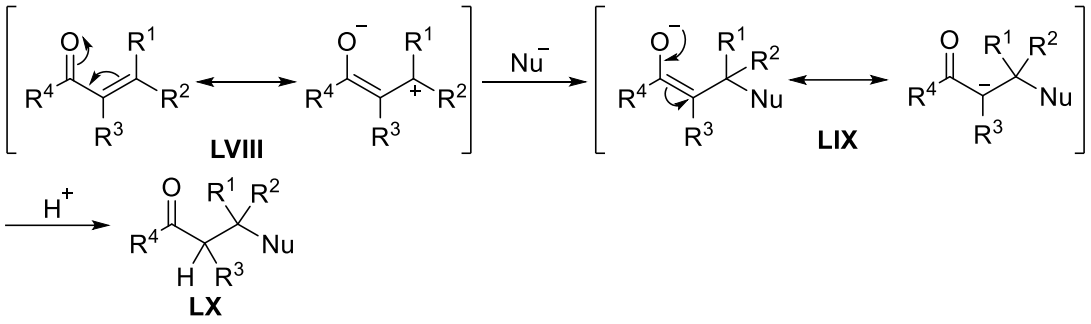
Dialkyl benzylidenemalonates are suggested to represent the lignan part in the stilbenolignan molecules. Benzylidenemalonates could be prepared by a Knoevenagel condensation, which is a modification of the aldol condensation. This is nucleophilic addition of an acidic carbonyl compound (**LII**) to the carbonyl group of aldehydes or ketones to form carbon-carbon double bond.[48] For example malonic esters can be used and piperidine (**LIII**) or other secondary amines together with an acid are used as catalysts to generate enol **LIV**, which subsequently reacts with the carbonyl group of **XLVI** and following elimination of water leads to an α,β-unsaturated carbonyl product **LVII** (**Scheme 1.8**).[50]



Scheme 1.8 Mechanism of the Knoevenagel condensation.

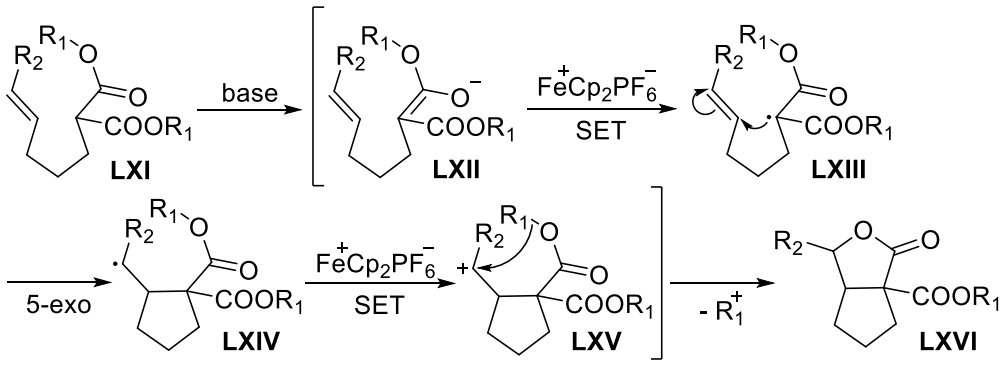
The connection between the stilbene unit and the dialkyl benzylidenemalonate is planned to be accomplished by nucleophilic conjugate addition. The organometallic nucleophilic compound may be generated by metal-halogen exchange from the halogenated stilbene. In this 1,4-addition, the nucleophile is added to a carbon-carbon

double bond conjugated with a carbonyl group. First, a bond is formed between the electrophilic β-carbon of the α,β-unsaturated compound **LVIII** and the nucleophile, and enolate **LIX** is generated as an intermediate, which is subsequently protonated on the α-carbon to form saturated 1,4-adduct **LX** (**Scheme 1.9**).[48]



Scheme 1.9 Mechanism of the 1,4-addition to α,β-unsaturated compound.

Oxidative radical cyclization of the resulting 1,4-adduct is suggested as the next step of this cascade, because it is one of the most applied methods for the construction of the cyclopentane core. In the reaction, an enolate **LXII** is generated from dicarboxylated compound **LXI** by deprotonation.[51] Ferrocenium hexafluorophosphate may be used as an oxidant to generate α-carbonyl radical **LXIII** by single electron transfer. The radical **LXIII** cyclizes in the very facile 5-exo-trig mode and it results in the stabilized radical **LXIV**.[52] Second equivalent of the ferrocenium salt causes next cyclization by the single electron oxidation of the radical **LXIV** to a carbocation **LXV,** which is stabilized by lactonization to form bicyclic lactone **LXVI** (**Scheme 1.10**).[53]



Scheme 1.10 Oxidative radical bicyclization of the dicarboxylated compound **LXI**.

The lactone resulting from oxidative bicyclization already contains the full skeleton of arylindane stilbenolignans. To finish the synthesis, the remaining ester group should be removed, and the lactone reduced to the tetrahydrofuran.

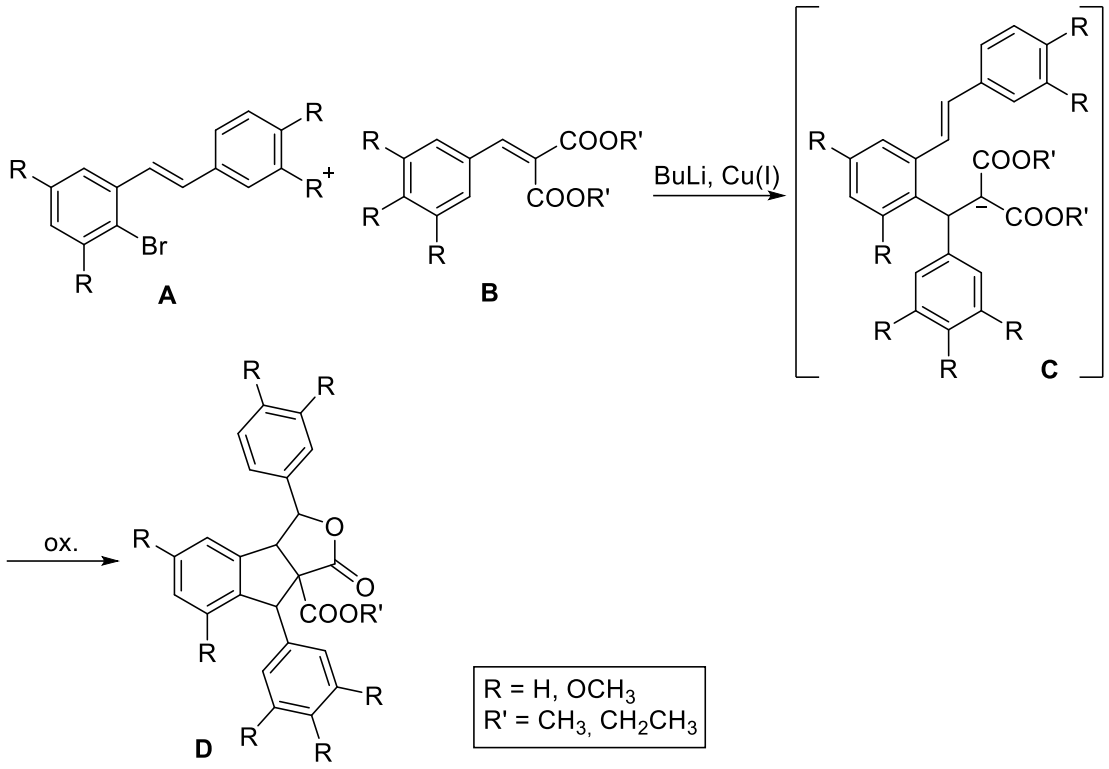
2 AIMS OF THE WORK

Arylindane stilbenolignans are natural compounds, which are challenging for synthesis with a structure including arylindane linked to a tetrahydrofuran and two more aryl groups. Although interesting biological activity has been proven for some representatives, little attention is generally paid to them in the literature.

The main aim of the work is to develop a new synthetic tandem method combining conjugate nucleophilic addition and oxidative radical cyclization. The motivation to develop a tandem process is mainly practicality. The number of isolation and separation steps is minimized in a tandem process, making the method faster and less laborious. In addition, the tandem process is more economic and environmentally benign by lowering solvent and reagent consumption.

Because two different reactions occur in one reaction mixture, it is obvious that optimization of conditions will be required. Therefore, another aim is to find such conditions that would be compatible with both 1,4-addition as well as bicyclization to obtain good overall yields.

Accomplishing the previous points will enable application of the tandem method to the preparation of the stilbenolignan natural compound. In the context of this thesis, it means finding an approach to the basic skeleton of stilbenolignans containing an arylindane unit bound to a tetrahydrofuran unit (**Scheme 2.1**, p. 23). After that, the synthetic effort should be focused the synthesis on selected stilbenolignans gnetifolin F, lehmbachol D and primarily kompasinol A, because this synthesis has not been accomplished yet.



Scheme 2.1 Planned tandem synthetic approach to arylindane stilbenolignans.

This synthetic approach is nature-inspired. Overall, the proposed synthetic approach follows the disconnection logic of the biosynthesis, however using intermediates in different redox state.

To optimize the synthetic method focusing more and more on stilbenolignans, starting materials (**A, B**) with increasing degree of oxygenation will be used. This will lead to production of various intermediates (**C**) and different analogues (**D**) of natural stilbenolignans. It should be possible to study the effect of the oxygenation pattern on the addition and following oxidative cyclization.

For the structural analogues of the target stilbenolignans, a biological activity similar to natural substances themselves may be expected.

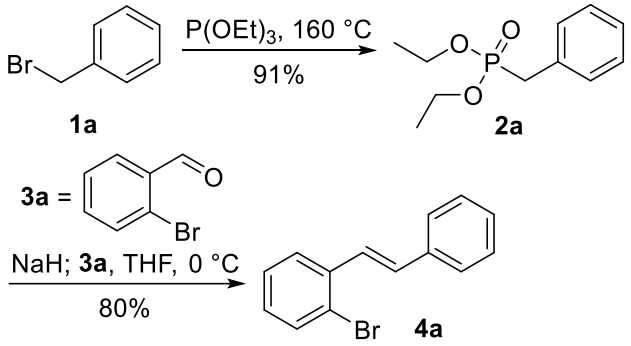
The stereostructure of gnetifolin F, lehmbachol D a kompasinol A has been determined only by NMR spectra and NOE experiments in publications. Therefore, another aim is to obtain indisputable proof of the relative configuration of the synthesized analogues by X-ray crystallographic analysis, which is a significantly reliable method of analysis than NOE difference spectroscopy. By comparing the NMR spectra of isolated natural stilbenolignans and their synthesized analogues the published configuration of mentioned compounds will be confirmed or disproved.

3 RESULTS AND DISCUSSION

3.1 Preparation of bromostilbenes and benzylidenemalonic esters

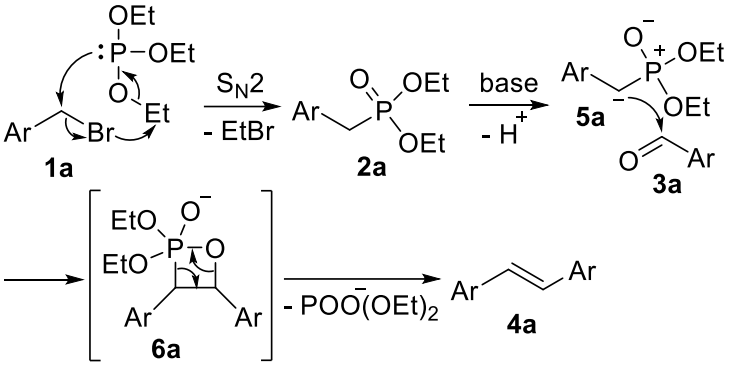
Two types of compounds were synthesized to serve as starting materials. Bromostilbenes were prepared by the Wittig or the Wittig-Horner reactions. Benzylidenemalonic esters were synthesized by the Knoevenagel condensation to represent the lignan part. Derivatives of these compounds with increasing number of methoxy groups were synthesized in order to study the behaviour of 1,4-addition and oxidative radical cyclization in the presence of additional oxygen atoms in the molecules and to develop a synthetic protocol for the construction of stilbenolignan analogues approaching the complex structure of the natural compounds.

(*E*)-1-Bromo-2-styrylbenzene (**4a**) was prepared as first representative of bromostilbenes (**Scheme 3.1**). Benzyl bromide (**1a**) reacted with triethyl phosphite forming 91% of diethyl benzylphosphonate (**2a**) by nucleophilic substitution. Phosphonate **2a** reacted with 2-bromobenzaldehyde (**3a**) in the presence of base by the Wittig-Horner reaction yielding 80% of **4a**.



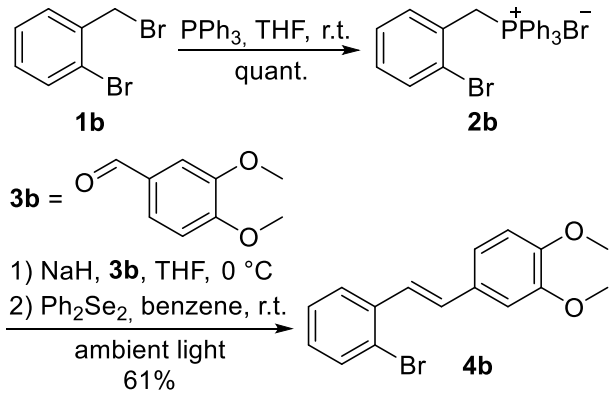
Scheme 3.1 Formation of **4a** by the Wittig-Horner reaction.

Mechanistically, the first step proceeds through the Michaelis-Arbuzov reaction, in which an S_N2 type alkylation of triethyl phosphite is followed by nucleophilic removal of the ethyl group to form **2a**. The mechanism of the Wittig-Horner reaction starts with deprotonation of phosphonate **2a** producing nucleophilic anion **5a**, which attacked the aldehyde **3a**. The resulting oxaphosphetane **6a** eliminated diethyl phosphate and formed **4a** (**Scheme 3.2**, p. 25).[48,54]



Scheme 3.2 Mechanism of the Michaelis-Arbuzov and the Wittig-Horner reactions leading to **4a**.

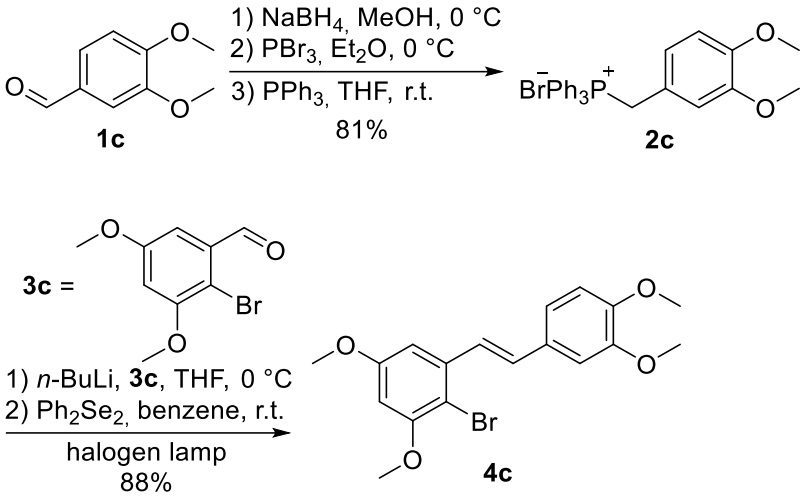
(*E*)-4-(2-Bromostyryl)-1,2-dimethoxybenzene (**4b**) was prepared as the second type of bromostilbenes. 1-Bromo-2-(bromomethyl)benzene (**1b**) reacted with triphenylphosphine to quantitatively generate (2-bromobenzyl)triphenylphosphonium bromide (**2b**) by an S_N2 reaction in the first step, which reacted with base and 3,4-dimethoxybenzaldehyde (**3b**) to produce a mixture of the (*E/Z*) stereoisomers of 4-(2-bromostyryl)-1,2-dimethoxybenzene. Subsequent equilibration with diphenyl diselenide led to the single (*E*) stereoisomer of **4b** in 61% yield (**Scheme 3.3**).



Scheme 3.3 Formation of **4b** by the Wittig reaction.

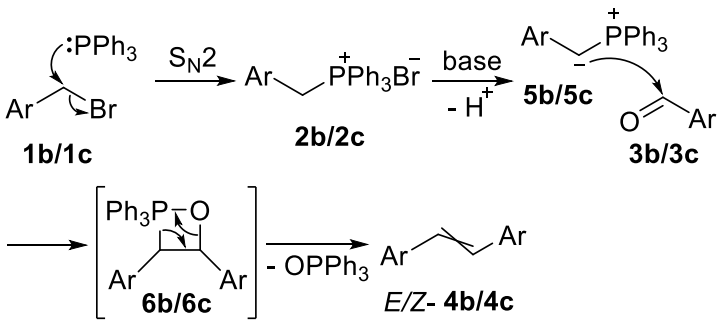
Another type of bromostilbene, tetramethoxy derivative **4c** was synthesized (**Scheme 3.4**, p. 26). In this case, 81% overall yield of the phosphonium bromide **2c** was obtained from 3,4-dimethoxybenzaldehyde (**1c**) by reduction with sodium tetrahydridoborate, bromination with phosphorus tribromide and subsequent S_N2 reaction with triphenylphosphine. After deprotonation by butyllithium, **2c** reacted with 2-bromo-3,5-dimethoxybenzaldehyde (**3c**) and the resulting mixture of (*E/Z*) stereoisomers of 2-bromo-1-(3,4-dimethoxystyryl)-3,5-dimethoxybenzene was

subsequently equilibrated with diphenyl diselenide to obtain a single (*E*) stereoisomer of **4c** in 88% yield.



Scheme 3.4 Formation of **4c** by the Wittig reaction.

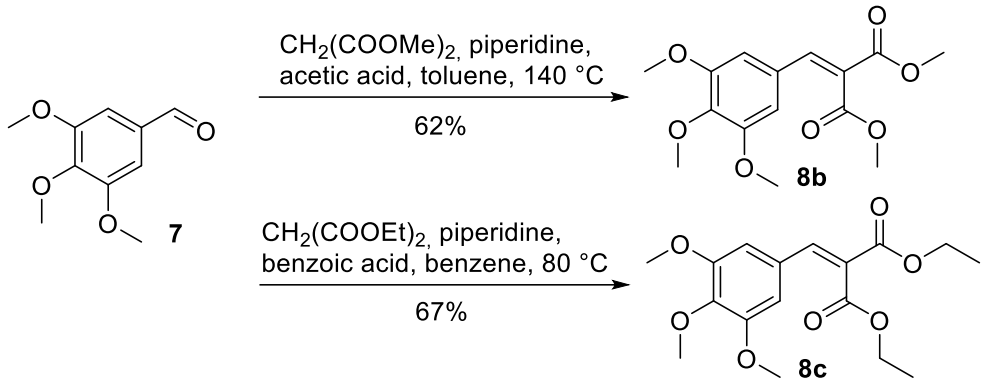
The first step of the formation **4b** or **4c** followed an S_N2 reaction mechanism, which is similar to formation of **4a**. But in these Wittig reactions, a triphenyl phosphonium ylide serves as nucleophile. Alkylation of triphenylphosphine generates phosphonium bromides **2b** or **2c**. Addition of base forms ylides **5b** or **5c**, which subsequently react with aldehydes **3b** or **3c**. The resulting oxaphosphetanes **6b** or **6c** eliminate triphenyl phosphine oxide and an (*E/Z*) mixture of stereoisomers of bromostilbenes **4b** or **4c** is produced (**Scheme 3.5**).[55]



Scheme 3.5 Mechanism of an S_N2 reaction and the Wittig reactions leading to an (*E*/*Z*) mixture of stereoisomers of **4b** and **4c**.

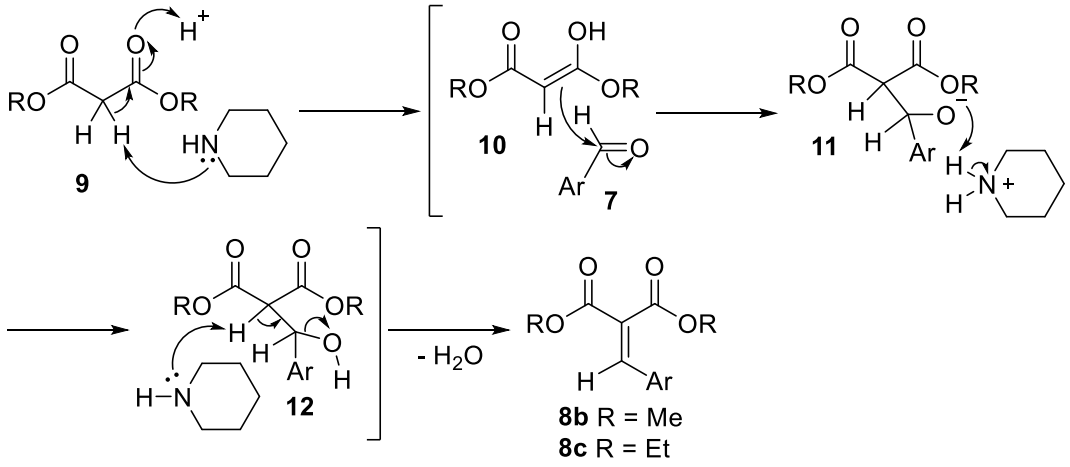
Benzylidenemalonic esters served as the second type of starting materials. The simplest Michael acceptor for conjugate addition optimization was the commercially available diethyl benzylidenemalonate **8a**. Oxygenated derivatives

dimethyl trimethoxybenzylidenemalonate (**8b**) and its diethyl analogue (**8c**) were prepared by the Knoevenagel condensation (**Scheme 3.6**). In these reactions, 3,4,5-trimethoxybenzaldehyde (**7**) reacted with malonic esters in the presence of piperidine and acid, which produced 62% of **8b** or 67% of **8c**, respectively.



Scheme 3.6 Formation of **8b** and **8c** by the Knoevenagel condensation.

The Knoevenagel condensation is one of the most common reactions used for the synthesis of α,β-unsaturated esters. This nucleophilic addition is catalyzed by piperidine and acids, that help enolize malonic ester **9**. The resulting enol form **10** reacts with the carbonyl group of aldehyde **7** to form α,β-unsaturated carbonyl compounds **8b** or **8c** via intermediates **11** and **12**, and water is eliminated (**Scheme 3.7**).[48,50]



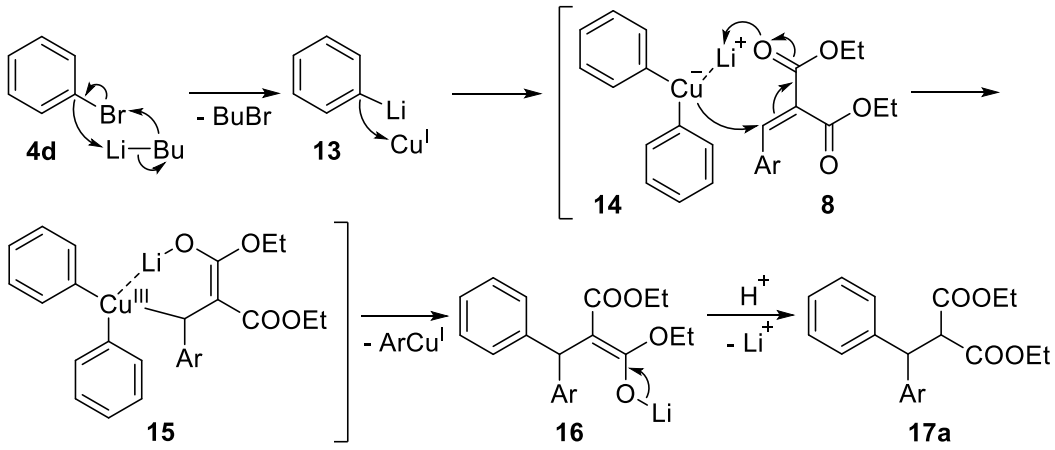
Scheme 3.7 Mechanism of the Knoevenagel condensation leading to **8b** and **8c**.

3.2 Conjugate additions of bromostilbenes to benzylidenemalonic esters

The proposed tandem annulation of bromostilbenes to benzylidene malonate esters starts with the generation of the very reactive aryllithium intermediates and their immediate conjugate addition. The tandem nature of the process requires this initial step to be as clean and as high yielding as possible in order to limit the amount of possible competing side-reactions in further steps. The conjugate addition was therefore optimized separately before moving on to further oxidation of the enolate.

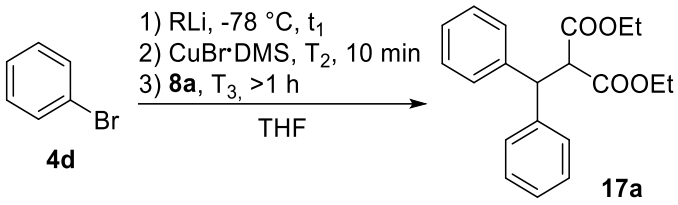
Commercially available bromobenzene (**4d**) and diethyl benzylidenemalonate (**8a**) were used as test substrates for the 1,4-addition. After that, bromostilbenes with increasing level of oxygenation and prepared benzylidenemalonic esters were applied and conditions of these reactions were optimized for each combination before the extending to the tandem oxidative radical cyclization process.

These series of reactions started with lithium-bromide exchange. In this reaction, bromobenzene **4d** with butyllithium generates organolithium compounds **13**, which subsequently reacts with a catalytic amount of a copper(I) salt to form lithium cuprates **14**. These organocopper reagents are soft nucleophiles, therefore they react at the β-position of α,β-unsaturated benzylidene malonic esters **8** by conjugate nucleophilic addition. The presumed mechanism, based on analogy with more intensively studied dialkylcuprates, involves generation of copper(III) species **15** followed by reductive elimination generating enolate **16** that upon protonation furnishes benzhydrylmalonate **17a** (**Scheme 3.8**).[56,57]



Scheme 3.8 Proposed mechanism of the lithium-bromide exchange and the 1,4-addition leading to **17a**, which is same for the formation of **17b-17f**.

The optimization data for the copper catalyzed conjugate addition of bromobenzene (**4d**) to diethyl benzylidenemalonate (**8a**) leading to **17a** are summarized in **Table 3.1** (**Scheme 3.9**).



Scheme 3.9 Formation of **17a**.

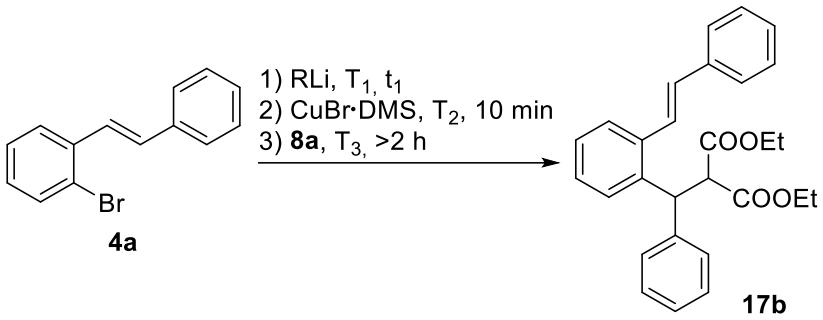
Table 3.1 Optimization of bromobenzene conjugate addition leading to **17a**. Equivalents (equiv.) based on **8a.**

Exp.	4d [equiv.]	R, [equiv.]	t_1 [min]	T_2 [°C]	T_3 [°C]	Yield [%]
A	1.2	*n*-Bu, 1.2	15	–40	–40 to r.t.	5
B	1.1	*n*-Bu, 2.6	15	–40	–40 to r.t.	8
C	1.3	*t*-Bu, 3.0	35	–40	–40 to 0	70
D	1.1	*t*-Bu, 2.6	10	r.t.	–40 to 0	74

In the experiments *A* to *D*, THF was used as solvent, because it is known to be suitable for cryogenic lithiation as well as conjugate addition and moderately compatible with the oxidative conditions of the following radical cyclization.[46,56,58] Two types of reagents for lithium-bromide exchange were used in this reaction series. *n*-Butyllithium reacted with **4d** in experiments *A* and *B, tert*-butyllithium was used in experiments *C* and *D*. Lithium was chosen for metallic-halogen exchange, because organolithium compounds belong to the most reactive available organometallic compounds, which can easily transmetallate to copper and other transition metals. From the available methods for metalation of arylhalides, it is the mildest in the sense, that it proceeds easily at low temperatures.[59] In the case of experiments *A* and *B*, when *n*-butyllithium was used, the yields were less than 10%. After work up, mostly unchanged starting materials were recovered. Isolation of **4d** means that *n*-butyllithium did not work, even increasing the excess did not help. Therefore, *n*-butyllithium was replaced with *tert*-butyllithium in larger excess in experiments *C* and *D*, where the yield exceeded 70%. The reason could be that *tert*-butyllithium is a better nucleophile and is

more reactive,[59] so organolithium **13** is faster generated. Moreover, a lower amount of *tert*-butyllithium and a shorter reaction time for the lithium-bromide exchange did not reduce yield. Cryogenic conditions are essential for the lithium-bromide exchange, because of high basicity of organolithium compounds and their limited stability in THF.[56] The catalyst copper(I) bromide-dimethyl sulfide complex was added to the reaction mixture from a special bent tube device that allows addition of solid reagents during the course of the reaction without opening the apparatus to air. Due to the catalytic amount of copper added, lithium diarylcuprates were generated to react with the β-position of benzylidenemalonate esters **8**. The cuprates are usually stable at low temperature, therefore organolithium-copper reagent **14** was formed at −40 °C in experiments *A*, *B* and *C*. Only in the case of *D*, the reaction with copper(I) salt was stirred at room temperature, but the yield was not significantly changed compared to experiment *C*. This means that the increase of temperature during formation of the lithium cuprate had an insignificant influence. Careful control of the reaction temperature is usually important for the desired 1,4-selectivity, therefore, benzylidenemalonic ester **8a** was added at −40 °C and the reaction mixture was subsequently slowly warmed to room temperature. The reactions were monitored by TLC, and when no further changes could be observed after one hour, the reactions were stopped. The reaction conditions used in experiment *D* leading to 74% yield of **17a** were considered optimal and used as a starting point for conjugate addition reactions of substrate **4a**.

In the next set of the reactions, (*E*)-1-bromo-2-styrylbenzene (**4a**) was used as starting material instead of bromobenzene (**4d**) and other reagents such as butyllithium, the copper(I) bromide-dimethyl sulfide complex and **8a** remained the same as in the first reaction series. This led to formation of 1,4-adduct **17b** (**Scheme 3.10**, p. 31). A somewhat different behaviour during the addition the of substrate **4a** compared to model bromobenzene (**4d**) was observed (**Table 3.2**, p. 31).



Scheme 3.10 Formation of **17b**.

Table 3.2 Conditions of the synthesis of **17b**. Equivalents (equiv.) based on **8a.**

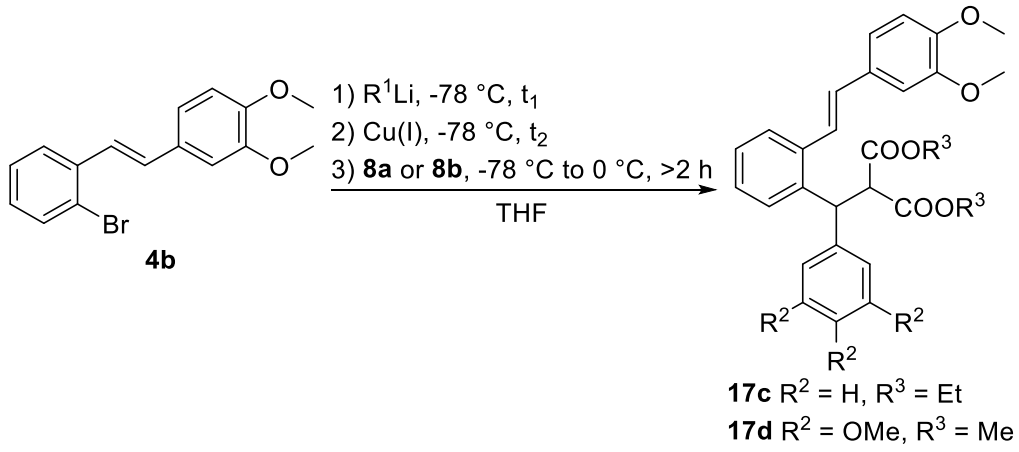
Exp.	Solvent	4a [equiv.]	R, [equiv.]	T_1 [°C]; t_1 [min]	T_2 [°C]	T_3 [°C]	Yield [%]
E	THF	1.6	*t*-Bu, 3.5	−78 to r.t.; 35	−40	−40 to r.t.	70
F	THF	1.2	*n*-Bu, 1.2	−78; 15	−78	−40 to r.t.	30
G	THF[1]	1.6	*t*-Bu, 3.5	−78 to r.t.; 25	−40	−40 to r.t.	-
H	DME	1.6	*t*-Bu, 3.5	−78; 10	−78	−78 to 0	-

[1]degassed

In experiment *E*, a combination of conditions from experiments *C* and *D* was applied except for the temperature during the lithium-bromide exchange, where *tert*-butyllithium was added at −70 °C, but the reaction was subsequently stirred at room temperature. The conditions of experiment *E* led to 70% yield of **17b**. In experiment *F*, *n*-butyllithium was used as reagent to compare the reactivity of **4a** and **4d** in the lithium-bromide exchange. In this case, a 30% yield of the 1,4-adduct was found, which is much more than in experiments *A* and *B*, where *n*-butyllithium was not satisfactory. Degassed THF was used as solvent in the experiment *G*. In this case, product **17b** was not isolated. The reason is currently unknown, however an error during manipulation of the frozen dry solvent cannot be excluded. A different solvent was used in experiment *H*, when the reaction took place in DME, but 1,4-adduct **17b** was not isolated as well. The reason is probably the ability of DME to form chelate complexes with cations,[60] which prevented formation of the lithium cuprate by complexation of the copper(I) ion, which could cause premature quenching. The highest

yield of this reaction series was obtained in the experiment *E*. The conditions of this experiment were considered as optimized.

In the next four experiments, the dimethoxy derivative of (*E*)-bromostilbene **4b** was used as starting material (**Scheme 3.11**). In three of them, **4b** reacted with butyllithium, copper(I) bromide-dimethyl sulfide complex and **8a** to obtain 1,4-adduct **17c**. In the fourth experiment, substrate **8a** was replaced with dimethyl 2-(3,4,5-trimethoxybenzylidene)malonate (**8b**) to form compound **17d**. Dimethyl benzylidenemalonate was used instead of the diethyl ester, because an S_N2 reaction is faster at less substituted carbon atoms because of steric repulsion in the tetracoordinate transition state, which can facilitate the planned decarboxylation at the end of stilbenolignan total synthesis.[61]



Scheme 3.11 Formation of **17c** and **17d**.

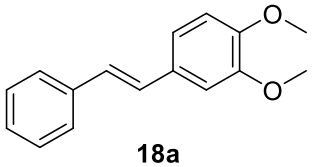
The conditions developed earlier on simpler substrates had to be again reoptimized for this new set of substrates (**Table 3.3**).

Table 3.3 Optimization of the synthesis of **17c** or **17**. Equivalents based on **8a** or **8b.**

Exp.	4b [equiv.]	R^1, [equiv.]	Cu(I)	R^2, R^3	t_1 [min]	t_2 [min]	Yield [%]
J	1.3	*t*-Bu, 1.1	CuBr·DMS	H, Et	40	15	68
K	1.3	*n*-Bu, 1.1	CuBr·DMS	H, Et	40	15	-
L	1.3	*t*-Bu, 1.3	CuBr·DMS	H, Et	15	5	98
M	1.3	*t*-Bu, 1.3	$LiCuBr_2$	OMe, Me	15	5	98

Besides using different staring material **8b**, this experiment was used to test a different form of copper catalyst, namely lithium dibromocuprate which is soluble in THF and can be added using a syringe. This change was made with regard to the tandem process, where the bent tube device could be preloaded with the oxidant and the reaction apparatus would not have to be opened.

In experiment *J* a small excess of starting material **4b** to *tert*-butyllithium was used and the temperature was kept at −78 °C, which was not changed until **8a** was added. The reaction was subsequently slowly warmed to 0 °C. These conditions afforded 68% of **17b.** In experiment *K*, *tert*-butyllithium was replaced with *n*-butyllithium and as a result, product **17b** was not detected, but starting material **4b** and stilbene **18a (Figure 3.1**) were isolated in ratio 2:1 from the resulting mixture. This means that the lithium-bromide exchange occurred with 66% conversion, but generated organolithium was not stable enough and was protonated before the conjugate addition. The origin of this different behaviour of stilbene **4b** derived organolithium in experiments *J* and *K* is not known.



18a

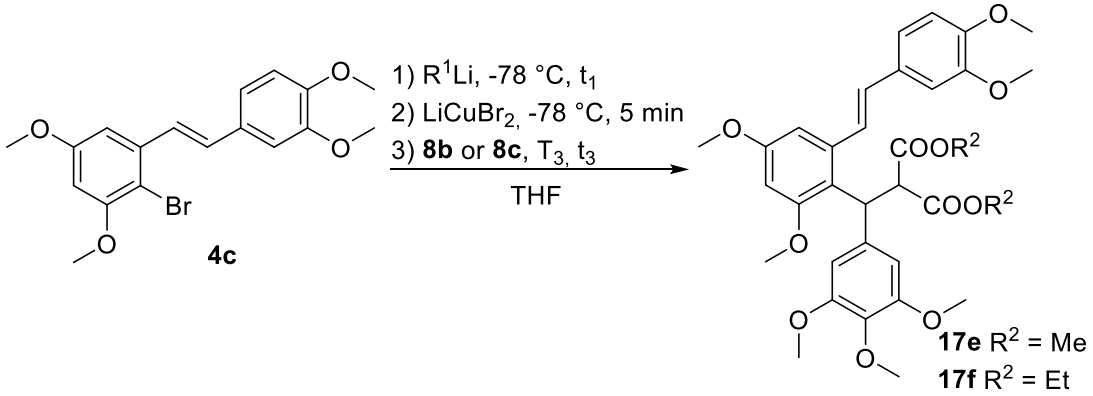
Figure 3.1 Structure of side product **18a**.

Recognizing the danger of quenching by the solvent, the reaction times for experiment *L* were reduced and the amount of *tert*-butyllithium increased to match the amount of aryl bromide. These conditions were also applied in experiment *M*, when substrate **8b** replaced **8a** and a different copper(I) salt was used. In both cases, the yield of reactions was 98%. Therefore, conditions of experiment *L* or *M* were considered as optimal for the formation of **17c** or **17d**, respectively.

In reaction series *A* to *H*, about two equivalents of *tert*-butyllithium based on **4** were used, but in this reaction set these reagents reacted in a ratio 1:1. In the literature, an excess of *tert*-butyllithium is recommended to avoid the reaction of the aryllithium with co-generated *tert*-butyl bromide, because the bromide reacts with excessing *tert*-butyllithium.[62] Unsatisfactory yields obtained in reactions *A* to *H* led to testing of lower amount of *tert*-butyllithium. Higher yields of **17** were obtained in experiments

J to *M*, in which a lower amount of *tert*-butyllithium was used. The reason may be that aryllithium is generated fast and co-formed *tert*-butyl bromide does not influence the reactivity of the aryllithium in the following steps, therefore an excess of *tert*-butyllithium is unnecessary. The excess may cause that unreacted *tert*-butyllithium remains in the reaction mixture and could react with intermediates generated in the following steps leading to low yields in the reactions *A* to *H*. Increasing the temperature to deactivate excess of *tert*-butyllithium cannot be used here, because the aryllithium is not sufficiently stable.

In a penultimate set of addition reactions, highly oxygenated (*E*)-bromostilbene **4c** reacted with butyllithium, $LiCuBr_2$ and **8b** to produce adduct **17e** (**Scheme 3.12**). In this series, various combinations of conditions were tested to find optimal ones (**Table 3.4**).



Scheme 3.12 Formation of **17e** and **17f**.

Table 3.4 Optimization of **17e** synthesis. Equivalents (equiv.) based on **8b.**

Exp.	4c [equiv.]	R^1, [equiv.]	t_1 [min]	t_3 [h]	T_3 [°C]	Yield [%]
N	1.3	*t*-Bu, 1.3	25	2	−78 to r.t.	34
O[1]	1.3	*t*-Bu, 1.3	5	21	−78 to 40	11
P[2]	1.3	*t*-Bu, 1.3	15	24	−78 to r.t.	47
Q[3]	1.3	*t*-Bu, 1.3	15	21	−78 to r.t.	23
R[4]	1.3	*t*-Bu, 1.3	5	5	−78 to 0	25
S[1]	1.3	*n*-Bu, 1.3	5	17	−78 to r.t.	16
T	1.3	*t*-Bu, 1.3	5	24	−78 to r.t.	51

[1]THF was degassed by bubbling of N_2.
[2]TMEDA (1.0 equiv.) was added after **8b** at -40 °C.
[3]TMEDA (1.0 equiv.) was added with *t*-BuLi at -75 °C.
[4]TMEDA (1.3 equiv.) was added with *t*-BuLi at -75 °C and HMPA (1.3 equiv.) added with **8b**.

The conditions for experiments *L* and *M* were applied to the experiment *N* except for longer lithiation time, which led to 34% yield of **17e**. From the resulting mixture, stilbenes **18b** (47%) and **18c** (7%) were also detected (**Figure 3.2**). Side product **18b** shows the instability of generated organolithium and compound **18c** maybe indicated an undesired reaction of organolithium with oxygen present in the solvent.

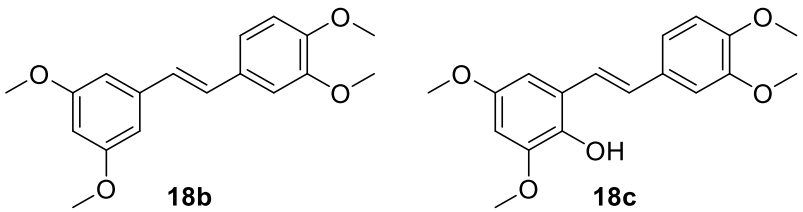


Figure 3.2 Structure of side products **18b** and **18c**.

Based on that, the amount of oxygen in THF was reduced by bubbling dry nitrogen through the solvent for several minutes and reaction time was reduced in experiment *O*. Only half of the amount of **18c** was isolated, but the amount of **18b** increased and **17e** was obtained in only 11% yield. This means that the presence of oxygen in solvent did not have significant influence on the reaction. It was theorized, that the low yield may be caused by an increased tendency of highly oxygenated aryllithiums toward aggregation or by product inhibition caused by aggregation phenomena. Therefore, in the next three experiments *P*, *Q* and *R*, TMEDA was added as an additive, which is a good ligand for metallic ions such as lithium(I) and copper(I). The combination of TMEDA with *tert*-butyllithium increases the reactivity and selectivity of lithiation.[63] In addition HMPA was used in experiment *R*, which has similar affinity to mentioned ions and causes breaking up oligomers of lithium bases.[64,65] However, the yield of **17e** in experiment *P* was only 47% and experiments *Q* and *R* yielded about 25% of **17e**. Another solution was replacing of *tert*-butyllithium with *n*-butyllithium to find out if *t*-butyl reacted with other reagents after lithium-bromide exchange, this was done in experiment *S*, but it afforded only 16% of **17e**. The conditions from experiment *P* were applied without using TMEDA, but with shorter time of lithiation in the last experiment *R*, where 51% of **17e** were obtained, which was the best yield of this reaction series.

In the last set of the 1,4-addtion reactions, substrate **8b** was replaced with **8c** in which the methyl ester groups were replaced with ethyl ester groups with less tendency to coordinate ions due to steric effects and to facilitate identification of products in

NMR spectra. Other reagents were used as in previous experiments *N* to *T* and led to formation of product **17f** (**Scheme 3.12**, p. 34). Reaction conditions were optimized for this combination of substrates **4c** and **8c** (**Table 3.5**).

Table 3.5 Optimization of **17f** synthesis. Equivalents (equiv.) based on **8c.**

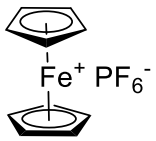
Exp.	4c [equiv.]	R_1 [equiv.]	t_1 [min]	t_3 [h]	T_3 [°C]	Yield [%]
U[1]	1.3	*t*-Bu, 1.3	5	16	−78 to 0	32
W	2.5	*t*-Bu, 2.5	5	5	−78 to −40	70
Y[2]	2.5	*t*-Bu, 2.5	5	4	−78 to −40	96
ZA[2]	1.5	*t*-Bu, 1.5	5	2	−78 to −40	30
ZB[2]	2.0	*t*-Bu, 2.0	5	2	−78 to −40	98

[1] TMEDA (1.0 eq.) was added after **8c**.
[2]Purified starting material **4c** was used.

In experiment *U*, TMEDA was used as additive and the reaction was quenched at 0 °C, all other reaction conditions similar to experiment *T* 32% of **17f** were obtained. This means that the reaction is independent of different benzylidenemalonic esters. The low reactivity of **4c** or the low stability of derived organolithium were overcome by increasing the amounts of reagents **4c** and *tert*-butyllithium in experiment *W*. The yield 70% of **17f** was obtained by quenching the reaction 5 h after addition of **8c** at −40 °C. The compound **4c** was initially stored at room temperature, but after a few days the originally colourless solid became darker. Therefore, compound **4c** was prepared again and purified by repeated recrystallization, which gave big colourless crystals. In experiment *Y*, thus prepared compound **4c** was used and conditions of reaction were similar to experiment *W* except of solvent, which was treated by a stream of dry nitrogen to eliminate traces of oxygen, which yielded 96% of **17f**. In the next experiment *ZA*, lower amounts of reagent **4c** and *tert*-butyllithium was used to verify the effect of purity on the yield, but again the reaction led to 30% of **17f**. This means that the low yields were not caused by impurities in **4c**. In the last experiment *ZB* of this reaction series, the same conditions were used as in the case of *Y* and *ZA* except for the amounts of reagents, where 2 equivalents of **4c** and *tert*-butyllithium based on **8c** were used. Experiment *ZB* gave yield 98% of **17f** and these conditions were considered as optimized.

3.3 Oxidative radical bicyclizations of in situ generated 1,4-adducts using ferrocenium salt

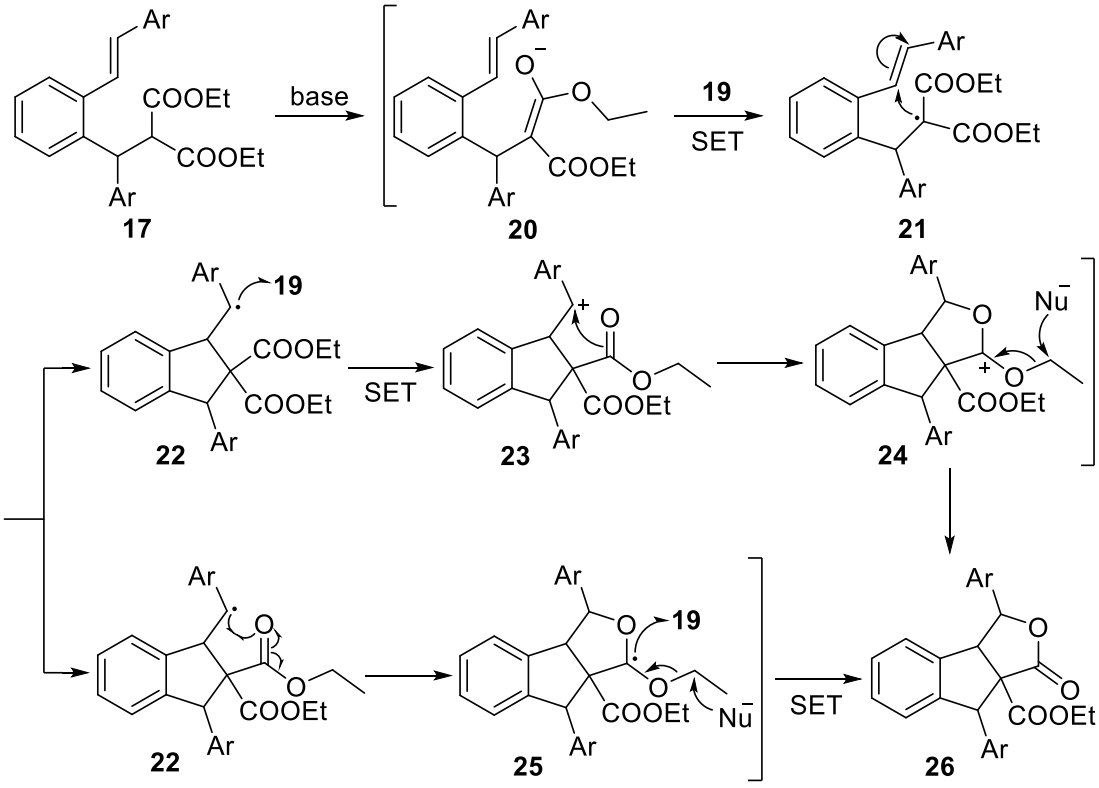
After optimizations of the 1,4-additions for each combination of substrates, the reactions were merged with oxidative radical cyclizations to the tandem processes. The cyclizations were induced by oxidant ferrocenium hexafluorophosphate (**19**) prepared according to the literature (**Figure 3.3**).[66]



19

Figure 3.3 Structure of oxidant **19**.

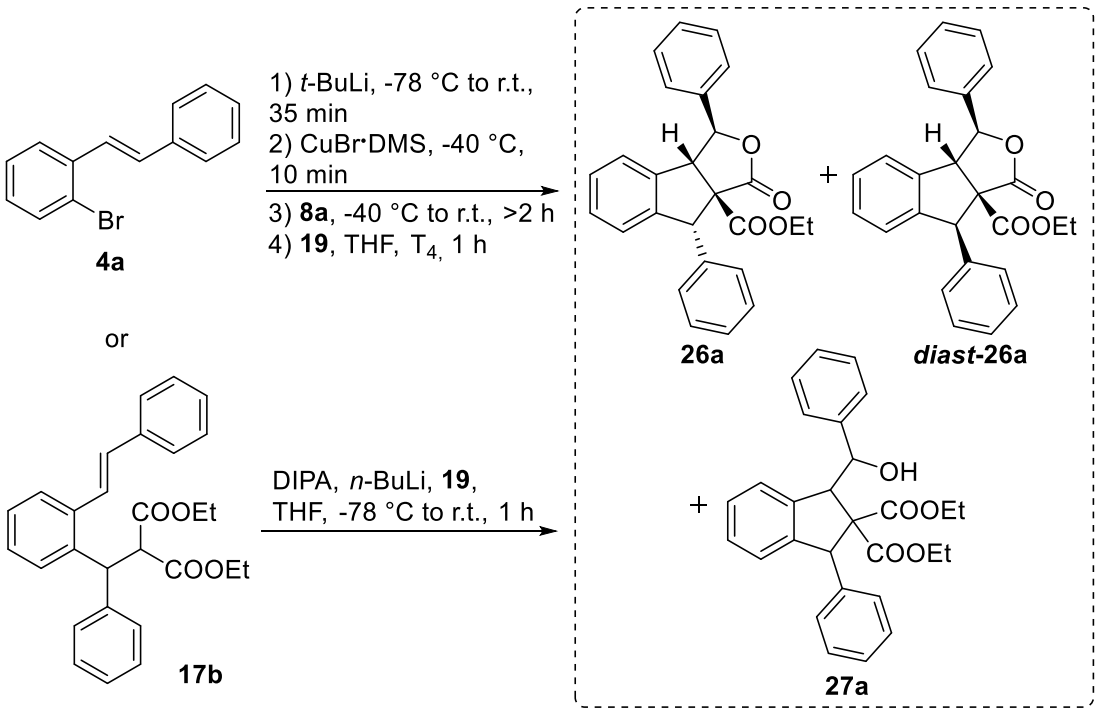
Oxidative radical cyclization is proposed as the method for the construction of full skeleton of arylindane stilbenolignans (**Scheme 3.13**).



Scheme 3.13 Potential mechanism of oxidative radical bicyclization of **17** leading to **26**.

In the first step, enolate **20** is formed either by deprotonation of 1,4-adduct **17** or directly by conjugate addition (**Chapter 3.2**). Subsequent oxidation by the ferrocenium salt **19** generates α-carbonyl radical **21** by single electron transfer. The cyclopentane core is formed by intramolecular 5-exo cyclization of radical **21**. The resulting stabilized benzyl radical **22** can be oxidized by a second equivalent of oxidant **19** to benzyl cation **23**, which cyclizes to form lactone **26** via intermediate **24**.[53] Another option is direct cyclization of **22** to intermediate **25**, after which a second single electron oxidation is followed by dealkylation to furnish lactone **26**.[67]

In experiment *E*, starting materials **4a** and **8a** were used to obtain adduct **17b** in 70% yield. This experiment was repeated with same reaction conditions, but ferrocenium hexafluorophosphate (**19**) was added as oxidant instead of aqueous quench (**Scheme 3.14**).



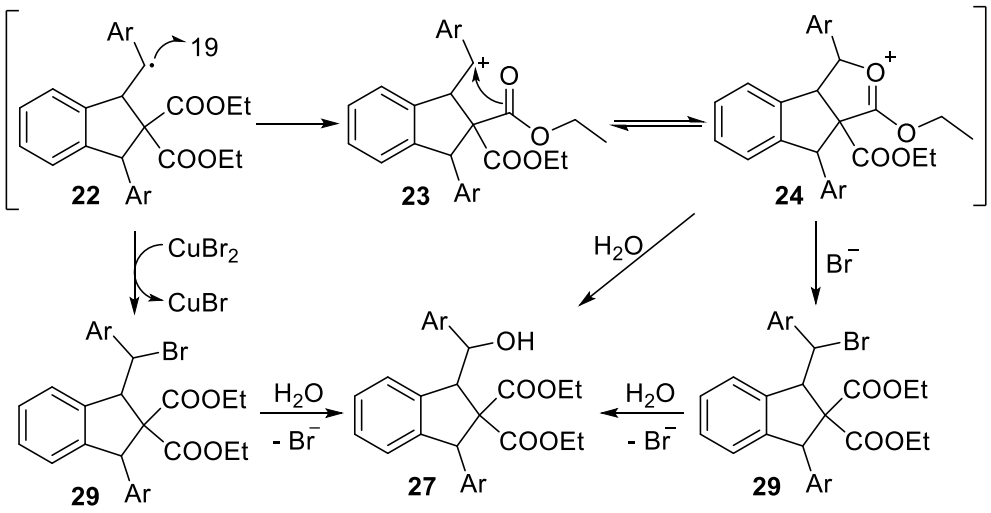
Scheme 3.14 Copper catalyzed conjugate addition of **4a** to **8a** and deprotonation of **17b** with subsequent oxidation by **19** leading to **26a**, ***diast*-26a** and **27a**.

Formation of **17b** by the 1,4-addition and cyclization were connected into the tandem process in experiments *I* and *II*, by contrast experiment *III* represented the stepwise process. The products of these experiments are summarized in **Table 3.6** (p. 39).

Table 3.6 Resulting compounds from oxidation of **17a**.

Exp.	Yield [%]		
	26a	***diast*-26a**	**27a**
I	53	7	-
II	19	2	17
III	11	2	15

In the first experiment *I*, conditions from experiment *E* were followed. Two hours after addition of **8a**, the reaction mixture was cannulated into the flask with oxidant **19** and the reaction was stirred 1 h at 0 °C. After work up, compounds **26a** and ***diast*-26a** were isolated in 53% and 7% yield. In the following experiment *II*, the same conditions as in experiment *I* were used, but oxidant **19** was added into the flask containing the reaction mixture, which yielded 19% of **26a** and 2% of ***diast*-26a**. Moreover, previously unobserved diastereomeric alcohol **27a** was isolated in 17% yield. In both experiments, the resulting reaction mixture contained less than 5% of the unoxidized 1,4-adduct **17b**. The yield of the first experiment was higher than in second one, the reason could be larger amounts of oxygen or water, which may have been introduced into the reaction during addition of the ferrocenium salt in experiment *II* which caused premature quenching. Their presence can also explain the formation of **27a**, when radical **22** is transformed by atom transfer from $CuBr_2$ directly to bromide **29**, which is hydrolysed during workup (**Scheme 3.15**).



Scheme 3.15 Potential mechanism of oxidative radical cyclization leading to **27**.

Another option leading to **27** is reaction of **22** with a second equivalent of **19**, which generates cations **23** or **24**. They may reacts with water to form compound **27** or with bromide ion from lithium-bromide exchange to generate bromide **29**, which in the presence of water leads to formation of **27** (**Scheme 3.15**, p 39).[53]

Compound **17b** isolated from experiments *E* and *F* was used in experiment *III*, in which DIPA and *n*-butyllithium were mixed to form LDA. After 20 min, **17b** was added into the reaction to generate enolate **20**, which subsequently reacted with oxidant **19**. This experiment *III* afforded 11% of **26a**, 2% of ***diast*-26a** and 15% of **27a**. The overall yield of this stepwise reaction was lower than those of experiments *I* and *II*.

Lactone **26a** was already prepared in Jahn's group by Mašek and was studied by NOE spectroscopy and X-ray crystallography analysis. These experiments afforded different determination of the relative configuration at C-3. The relative configuration determined by crystallography analysis is depicted in **Figure 3.4** and differs from the reported configuration of natural kompasinol A (**30**) at C-3 (**Figure 1.7**, p.16).

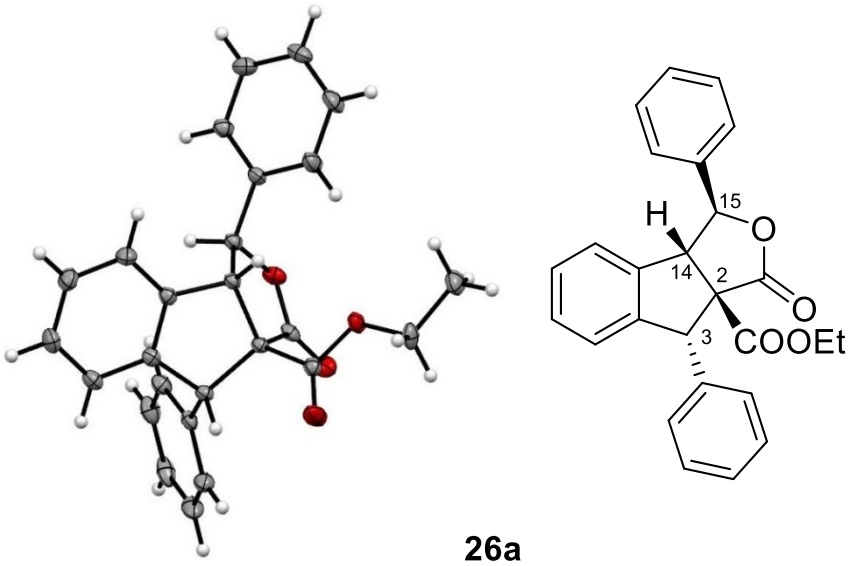


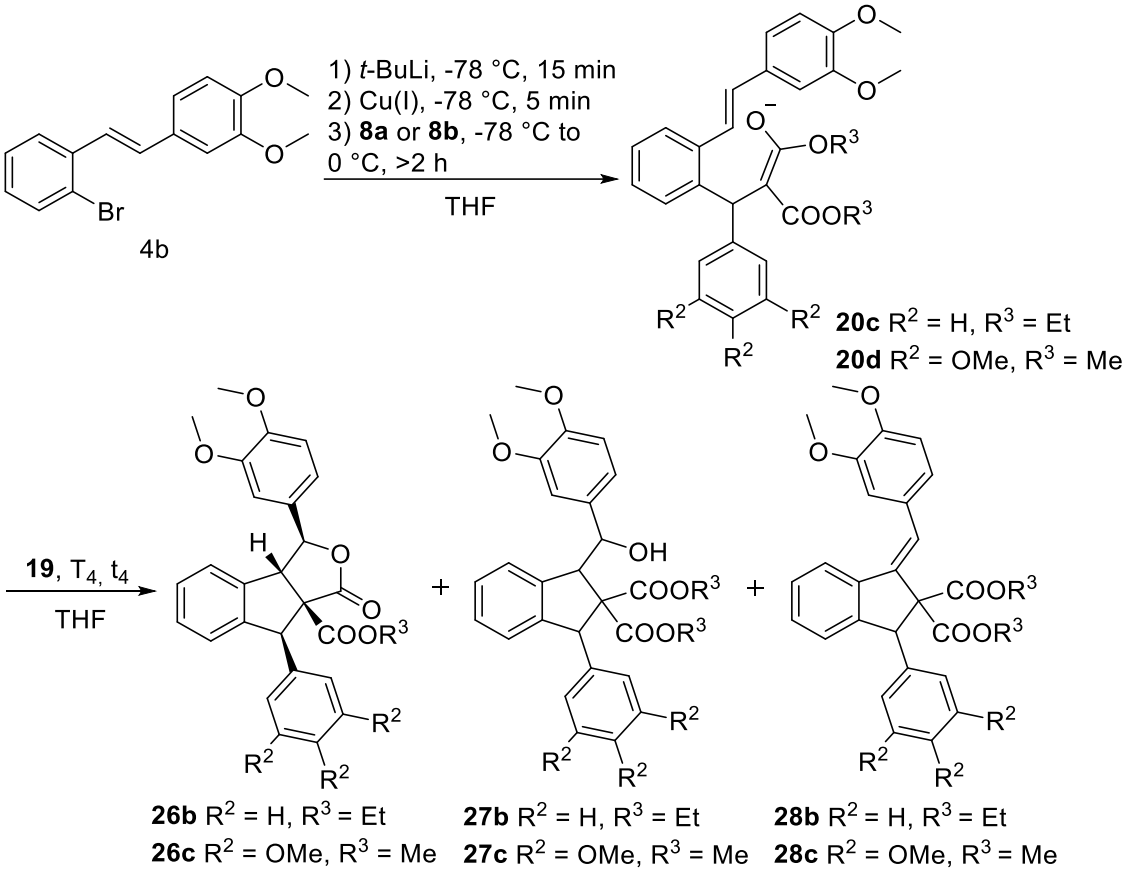
Figure 3.4 Crystal structure of **26a**.

The X-ray of **26a** shows *trans* configuration between H-14 and H-15 and *cis* configuration between H-3 and H-14. The phenyl group at position C-15 with H-14 and ester group at position C-2 are located above the arylindane plane, while the phenyl group at position C-3 is oriented below the plane of the tricycle.

The relative configuration of ***diast*-26a** (**Scheme 3.14**, p. 38) was determined later by the comparison with the ^{1}H and ^{13}C NMR spectra of **26d**, whose relative

configuration was determined by crystallographic analysis, which shows that the relative configuration of ***diast*-26a** is similar to kompasinol A.

The tandem method was also applied to substrates **4b** and **8a** or **8b**, where the 1,4-addition led to enolates of **17c** or **17d**, which were subsequently oxidized by ferrocenium salt **19** (**Scheme 3.16**).



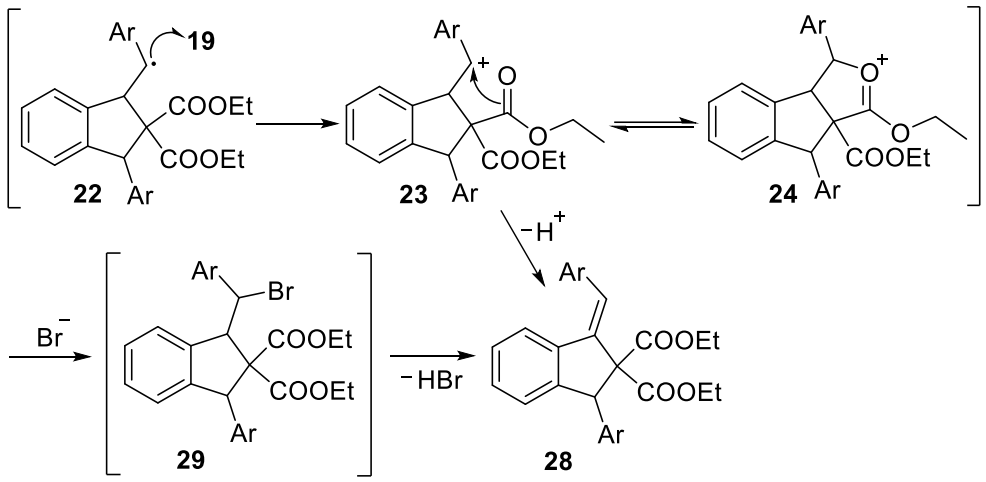
Scheme 3.16 Formation of **20c** and **20d** and subsequent oxidation by **19**.

Table 3.7 Oxidation conditions of enolates **20c** or **20d** and formed products.

Exp.	Cu(I)	R^2, R^3	T_4 [°C]	t_4 [min]	Yield [%]			
					17c/d	26b/c	27b/c	28b/c
IV	CuBr·DMS	H, Et	0 to r.t.	90	6	3	16	21
V	CuBr·DMS	H, Et	0	30	10	3	8	32
VI	$LiCuBr_2$	H, Et	0 to r.t.	90	22	-	31	18
VII	$LiCuBr_2$	OMe, Me	0	60	5	-	4	37

In experiment *IV*, the procedure from experiment *L* was followed and oxidant **19** was added by the bent tube device 2 h after addition of **8a** at 0 °C and the reaction was

warmed to room temperature and quenched after 90 min. The reaction apparatus was not opened during this experiment. Similar reaction conditions were used in experiments *V* or *VI*, but oxidant **19** was added directly into the temporarily opened flask at 0 °C. After 30 min or 90 min, respectively. The reaction was quenched at 0 °C or at room temperature. Experiments *IV*, *V* and *VI* afforded **17c** and alcohol **27b** and new type of product **28b** was isolated. Formation of alcohol **27b** probably was not connected to the amount of the oxygen, which got into the reaction during addition of the oxidant, because 18% of **27b** was produced without opening the flask in experiment *IV*. The real reason could be the presence of oxygen in the solvent. Formation of the alkene **28** may result either from direct loss of proton from cation **23** or may be the product of elimination of hypothetical bromide **29** during basic workup (**Scheme 3.17**).[53]



Scheme 3.17 Potential mechanism of the formation of **28**.

In experiment *VII*, conditions from experiment *M* were used and oxidant **19** was added from the bent tube device without opening the reaction apparatus at 0 °C and the reaction was quenched after 60 min. Alkene **28c** was isolated as the major product in this experiment together with minor amounts of **17d** and **27c**. In contrast to experiments *I* to *III*, lactones **26b** or **26c** were not isolated in experiments *VI* and *VII* and only a low amount of **26b** was isolated in experiments *IV* and *V*. The relative configuration of this lactone (**Scheme 3.17**) was determined later by the comparison of the ^{1}H and ^{13}C NMR spectra of **26d** as in the case of ***diast*-26a**. This proved that **26b** is analogue of ***diast*-26a** with the relative configuration similar to kompasinol A.

The relative configuration of alkene **28c** was determined by X-ray crystallographic analysis (**Figure 3.5**). The crystal structure **28c** shows a (*E)* configuration of a double bond between C-14 and C-15. The aryl group at position C-3 is located above the arylindane plane and the aryl group at position C-15 is also twisted above the plane.

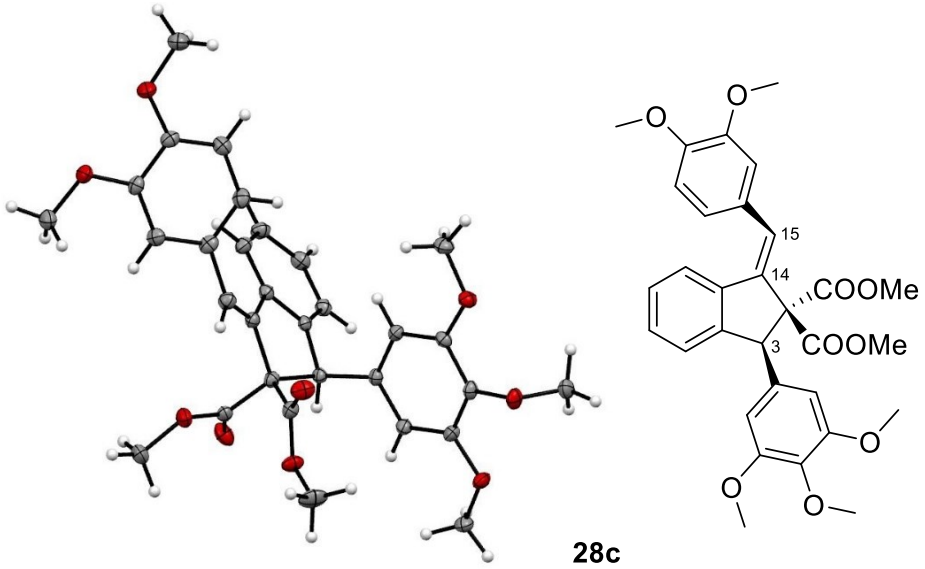


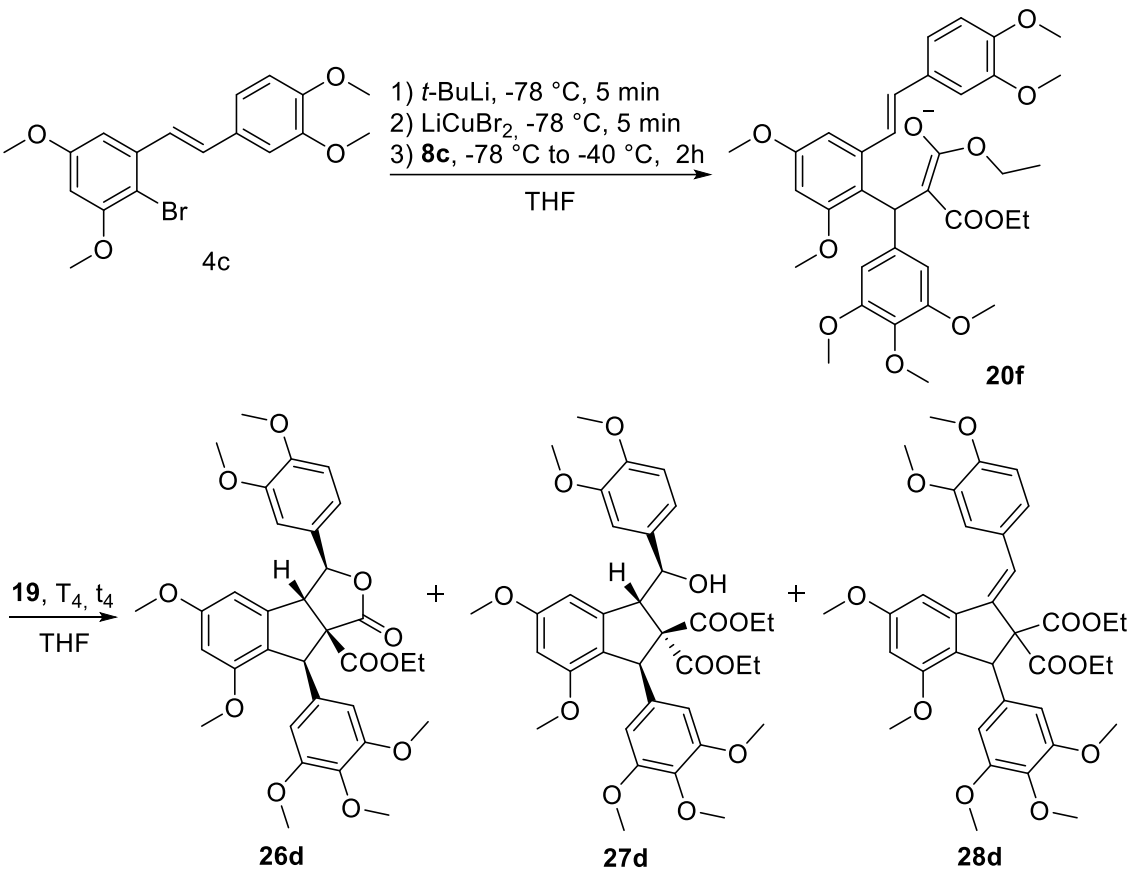
Figure 3.5 Crystal structure of **28c**.

According to the result, the configuration of carbon-carbon double bond of alkene **28b** was determined same configuration to **28c** by comparison of the ^{1}H and ^{13}C NMR spectra.

According to experiment *ZA*, starting materials **4c** and **8c** were used to prepare enolate **20f**, which was subsequently oxidized by **19** (**Scheme 3.18**, p. 44). In this series of tandem experiments, a mixture of compounds was produced and the yields with corresponding oxidation conditions are summarized in **Table 3.8**.

Table 3.8 Oxidation conditions of **20f** with corresponding products.

Exp.	T_4 [°C]	t_4 [h]	Yield [%]		
			26d	27d	28d
VIII	−40 to 0	2	75	4	-
IX	−40 to 0	2	54	17	15
X	−10 to r.t.	1.5	34	19	18



Scheme 3.18 Formation of **20f** and subsequent oxidation by **19**.

In experiment *VIII*, the procedure from experiment *ZB* was followed and oxidant **19** was added to the flask under counter current of nitrogen 1.5 h after addition of **8c** at −40 °C. The reaction was slowly warmed to 0 °C and quenched after 2 h. In this experiment, lactone **26d** was isolated as major product in 75% yield, 4% of alcohol **27d** was obtained and alkene **28d** was not isolated. In the following experiment *IX*, similar conditions were applied except for the addition of DIPA (0.5 equivalents based on 8c) 30 min after the oxidant, which led to 54% of **26d**, 17% of **27d** and 15% of **28d**. The change in the product ratio was probably caused by the presence of DIPA, which acted as a base and therefore increased the rate of deprotonation of the cation or bromide leading to alkene **28d**. In experiment *X*, similar conditions to experiment *VIII* were used, but ferrocenium salt **19** was added at −10 °C and the reaction mixture was warmed to 0 °C. This experiment afforded 34% of **26d**, 19% of **27d** and 18% of **28d**. Higher reaction temperature of oxidation thus probably made deprotonation of the cation or bromide faster. Compound **17f** was not detected in experiments *VIII, IX*

and *X*. The amount of **27d** had to be calculated from the ^{1}H NMR spectra of the crude mixture, because this compound undergoes lactonization to **26d** during isolation, this indicates identical relative configuration of **26d** and **27d**.

Lactone **26d** was isolated as major product in all three experiments and was studied by NOE spectroscopy and X-ray crystallography. The NOE experiment showed interactions between H-14 and H-20, which indicates *trans* orientation of H-14 and H-15. Missing interaction between H-14 and H-5 indicates a *trans* orientation of H-14 and the aromatic ring containing H-5 (**Figure 3.6**). X-ray crystallographic analysis unequivocally disproved this configuration assignment at C-3 establishing the relative stereochemistry between H-14 and H-3 to be *trans*. The relative configuration established by NOE proved to be wrong as in the case of compound **26a**. Therefore, the determination of the structure based only on NOE experiments must be considered questionable for this type of compounds.

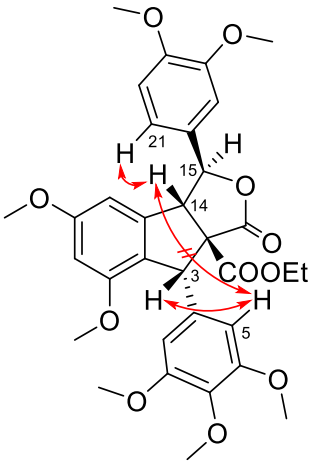


Figure 3.6 NOE of lactone **26d**.

The crystal structure of **26d** shows a *trans* configuration between H-3 and H-15 as well as between H-14 and H-15, which means that aryl groups at position C-3 and C-14 with ester groups at position C-2 and H-14 are located above the arylindane plane (**Figure 3.7**, p. 46).

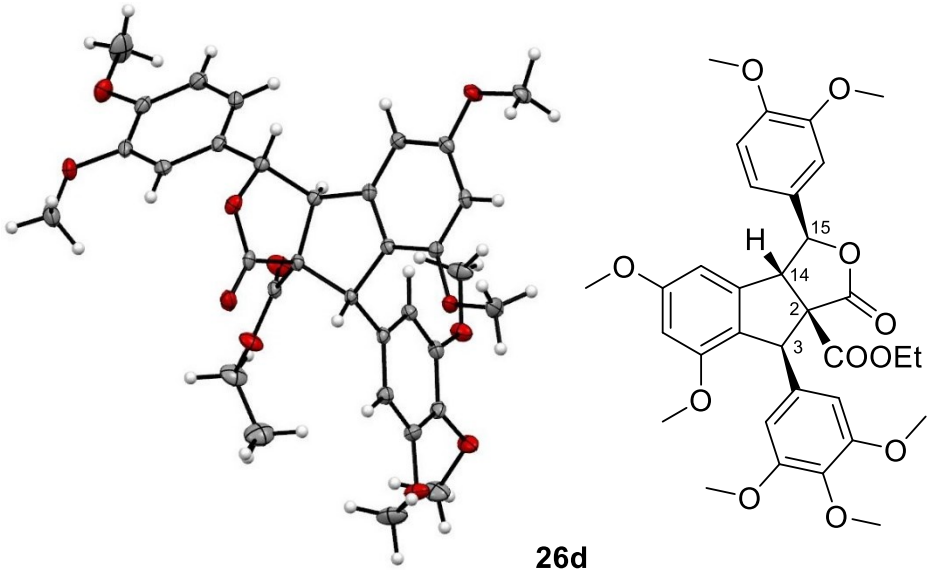


Figure 3.7 Crystal structure of **26d**.

Lactone **26d** was isolated in good overall yield and the structure except of remaining ester and carbonyl groups is similar to the permethylated derivative of kompasinol A **31** (**Figure 3.8**), which was prepared from isolated kompasinol A (**30**).[34] Moreover, the relative configuration of **26d** determined by X-ray crystallography is the proposed published relative configuration of kompasinol A (**30**). This shows the completion of the target tandem process development focusing on stilbenolignan analogues.

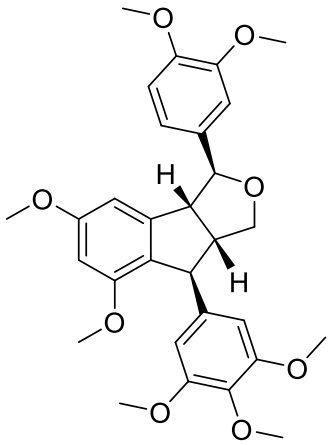
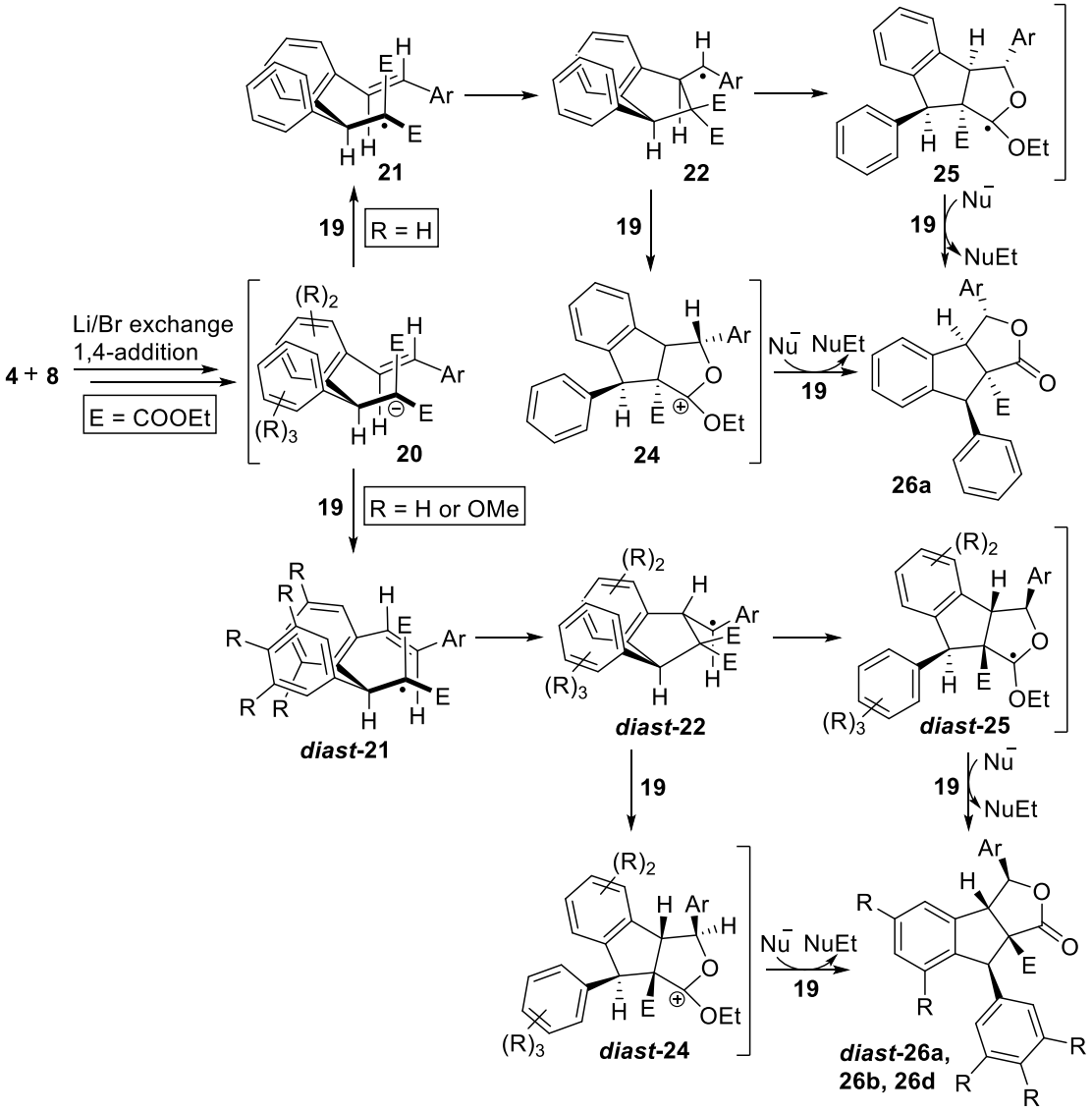


Figure 3.8 Relative configuration of **31**.

Planned decarboxylation and reduction of lactone of **26d** will allow comparison of the ^{1}H and ^{13}C NMR spectra with **30** and thus verify similarity of the relative configurations of decarboxylated and reduced **26d** with **30** or **31**.

The diastereoselectivity of the lactone formation depends on a double bond configuration and also on presence of substituents on aryl groups. After conjugate addition of substrates **4** and **8**, the enolate **20** is generated, which is subsequently oxidized by **19** to form radical **21**. Configuration of radical **21** in a chair-type transition state plays key role in the relative configuration of resulting lactone **26** and depends on steric repulsion between aryls sharing position C-3 (**Scheme 3.19**).



Scheme 3.19 Diastereoselectivity of oxidative radical cyclization.

If there are no substituents, steric irradiation between aryls is lower and configuration change of radical **21** is not required and benzyl radical **22** is generated by 5-exo cyclization. After formation of the cyclopentane core, the relative configuration is determined and is not changed during following steps. The benzyl radical **22** lactonizes

to radical **25** and is oxidized by **19** or is directly oxidized by **19** to form carbocation **24**, but in both cases ethyl group is eliminated and the lactone **26a** is generated as racemate. The relative configuration of **26a** was not observed in methoxylated analogues.

The relative configuration of ***diast*-26a**, **26b** and **26d** is determined after formation of **21**, where presence of substituents caused change of configuration due to aryl irradiation and ***diast*-21**, which differs from **21** by position of H-14 and aryl group at position C-15. Subsequently, ***diast*-21** cyclizes in 5-exo-trig mode and benzyl radical ***diast*-22** is generated. After lactonization, oxidation and dealkylation steps the lactone is formed and its relative configuration corresponding to ***diast*-26a**, **26b** and **26d** differs from **26a** by aryl group at position C-3, which is located in different plane to H-2, H-14 and aryl group at position C-15.

To conclude the previous experiments, some trends were observed during both addition and oxidation experiments related to an increasing number of oxygen atoms contained in the starting materials. First, the yields of 1,4-addition increased with increasing level of substrate oxygenation until oxygen in molecule caused metal coordination, which probably produced unreactive complexes (experiments *N* to *T*). Next, according to the reaction mechanism, three types of products were detected. The ratio varies depending on the degree of oxygenation. The yield of lactone decreased in the reactions of **4b** compared to **4a** but yield of alcohol and alkene increased. When **8b** was used as starting material, lactone **26c** was detected in 3% yield and **26b** was not detected, and yield of the alcohols **27c** and **27b** decreased, but alkenes **28c** and **28b** were isolated as major product. On the contrary, lactone **26d** was produced as major product and yield of alcohol and lactone decreased in the case of substrates **4c** and **8c**. The formation of lactones or alkenes do not depend just on oxygenation level of both substrates, but also on the type of benzylidenemalonic esters.

A benefit of the described tandem process was the selectivity of each reaction step, which was ensured by the carbon oxidation state changes during the process, this prevented the formation of side products. At first, the generated organolithium selectively reacted with the β-position of the α,β-unsaturated compound to form the 1,4-adduct. α-Carbonyl radicals were generated and reacted with a double bond of stilbene moiety to form cyclopentane core by 5-exo intramolecular cyclization. Finally, resulting benzyl radical or carbocation attacked carbonyl group to from lactone.

4 CONCLUSION

The development of a new tandem process was planned and successfully carried out by the combination of nucleophilic conjugate addition and oxidative radical cyclization. This tandem method did not produce a large number of side products, because the selectivity was ensured by the formation of intermediates with different carbon oxidation states, which selectively reacted with different functional groups during the process.

An effective approach to the basic stilbenolignan skeleton was found by the development of this tandem method. Stilbenes and benzylidenemalonic esters with different level of oxygenation were prepared and applied as starting materials in this tandem process, which led to arylindane derivatives approaching natural stilbenolignans. The synthetic effort was focused primarily on kompasinol A and this aim was almost carried out, because compound **26d** has the relative configuration and structure corresponding to published permethylated derivative of kompasinol A except for the additional lactone and ester groups.

Different reaction conditions were used during the development of this tandem method. These conditions had to be optimized dependently on oxygenation degree of starting materials. During the optimization of conjugate additions itself and tandem processes, six 1,4-adducts and eleven oxidation products were synthesized. The highest yield of this tandem processes was obtained in the case of the most oxygenated substrates **4c** and **8c**, which was in average 78%, also the selectivity leading to formation of lactone **26d** was the highest in this case. Moreover, the relative configuration of **26d** is same as published configuration of target kompasinol A.

The oxygenation pattern for the addition and following oxidative cyclization was studied, because starting materials with increasing number of methoxy groups (**4a**, **4b**, **4c**, **8a**, **8b**, **8c**) were used. It was found that the yields of 1,4-additions increased with increasing level of substrate oxygenation until oxygens in **4c** with **8b** or **8c** caused metal coordination which probably produced non-reactive complexes. The tandem processes afforded three types of products – lactones (**26a**, ***diast*-26a** **26b**, **26c**, **26d**), 4-hyroxyesters (**27a**, **27b**, **27c**, **27d**) and unsaturated diesters (**28a**, **28b**, **28c**). Their ratio varied depending on the oxygenation level of both substrates and on the type of benzylidenemalonic esters.

The biological activity of the structural stilbenolignans and their analogues similar to the natural substances has not been proven, because synthetic material has so far not been accessible.

The last aim of this thesis was the determination of the relative configurations of gnetifolin F, lehmbachol D and kompasinol A by the comparison of the NMR spectra with synthesized analogues, because their configuration has been determined only based on NOE experiments. This aim was not possible to accomplish, because the most similar synthesized analogue **26d** contains additional carbonyl and ester group and the comparison with NMR spectra of natural compounds may lead to incorrect results. Therefore, the true relative configuration of gnetifolin F, lehmbachol D and kompasinol A is still a question. However, it was shown for two examples **26a** and **26d** that the relative configuration determination based on NOE experiments is not reliable. The here reported investigations pave however the way for unambiguous determination of the absolute and the relative configuration of a major class of stilbenolignans.

5 EXPERIMENTAL PART

5.1 General experimental conditions and used instruments

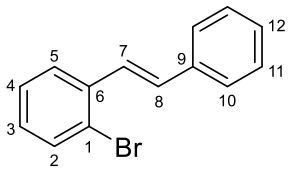
Weight of samples was measured on a precision balance (Kern, PLJ SIO-3M) and analytical balance (Kern, ALJ 220-4M). All reactions were conducted in oven-dried or heat gun-dried glassware under a nitrogen atmosphere and were stirred by magnetic stirrer (IKA, RCT classic). Solvents DCM, DME, EA, THF, hexane and toluene were dried following standard method under an argon atmosphere. TLC plates Silica gel 60 F_{254} (Merck KGaA) with UV indicator were used for reaction monitoring. Flash column chromatography separations were performed on silica gel 60 (Fluka, 230-400 mesh) and solid samples were loaded by adsorption on Celite®. Solvents from samples were evaporated on rotary evaporator (Heidolph, Laborota 4000 efficient). Melting point of solid samples was measured on digital melting point apparatus (Stuart, SMP 10). The structures of all isolated products were determined using spectral analysis. ^{1}H and ^{13}C NMR spectra were measured on the Bruker, Avance 400 MHz NMR spectrometer. $CDCl_3$ was used as a standard for ^{1}H NMR (δ = 7.26) and ^{13}C NMR (δ = 77.36). ^{13}C NMR assignments were obtained from APT experiments. More information about structures was obtained from COSY, HMBC and HSQC experiments. IR spectra were recorded on a FT-IR spectrometer (Bruker, ALPHA) using an ATR device. Two types of ionization were used to obtain mass spectra in the laboratories of IOCB CAS Prague. EI mass spectra were obtained on a Waters GCT Premier spectrometer at 70 eV and ESI spectra were measured on Thermo Fisher Scientific LCQ Fleet spectrometer, sample concentration approx. 1µg/mL. MS spectra with high-resolution were obtained on a Waters Q-Tof micro spectrometer. X-ray crystallographic analyses were executed by Dr. Ivana Císařová at the Department of Inorganic Chemistry, Charles University.

5.2 Procedures and analytical data

5.2.1 Preparation of substituted bromostilbenes and benzylidenemalonic esters

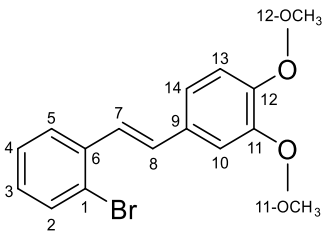
In this section, structures are numbered using a system unified with the rest of this thesis, in which atoms retain their numbers in benzylidene malonic ester units over the whole synthetic sequence. Numbering of stilbenes starts from the atom, which is connected to the benzylidene malonate unit in conjugate addition and after this connection, numbering of the stilbene part starts from 8. This numbering system is not consistent with systematic numbering according to IUPAC, but adds comparability of data.

(*E*)-1-Bromo-2-styrylbenzene (4a):



The compound was prepared according to the literature in 73% yield as a colourless oil.[68] **R_f** = 0.33 (hexane); **IR ν [cm^{-1}]:** 3023 (w), 1629 (w), 1598 (w), 1585 (w), 1559 (w), 1493 (m), 1464 (m), 1447 (m), 1434 (m), 1257 (w), 1216 (w), 1113 (w), 1023 (s), 957 (s), 753 (vs), 706 (s), 687 (s), 672 (s), 547 (m); **MS EI+ *m/z*, (%):** 260/258 (63, $[M]^{+\bullet}$), 179 (97, $[M–Br]^{+}$), 178 (100, $[M–HBr]^{+\bullet}$); **HRMS EI+ *m/z*:** $[M(^{79}Br)]^{+\bullet}$ Calcd.: 258.0044; Found: 258.0043; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.68 (dd, *J* = 7.9, 1.6 Hz, 1H, CH-2), 7.60 (d, *J* = 8.2 Hz, 1H, CH-5), 7.57 (d, *J* = 7.6 Hz, 2H, CH-10), 7.49 (d, *J* = 16.2 Hz, 1H, CH-7), 7.40 (t, *J* = 7.5 Hz, 2H, CH-11), 7.34-7.29 (m, 2H, CH-4, CH-12), 7.13 (td, *J* = 7.7, 1.6 Hz, 1H, CH-3), 7.06 (d, *J* = 16.2 Hz, 1H, CH-8); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 137.3 (s, C-6/C-9), 137.1 (s, C-6/C-9), 133.2 (d, C-5), 131.6 (d, C-8), 128.92 (d, C-3), 128.87 (d, C-11), 128.2 (d, C-4/C-12), 127.7 (d, C-4/C-12), 127.6 (d, C-7), 127.0 (d, C-10), 126.8 (d, C-2), 124.3 (s, C-1).

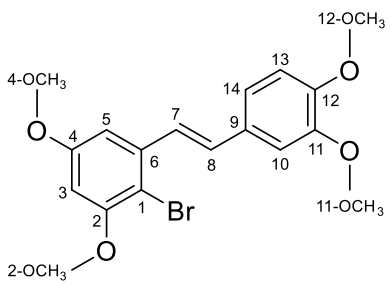
***(E)*-4-(2-Bromostyryl)-1,2-dimethoxybenzene (4b):**



The synthesis is based on the published approach to the non-methoxylated analogue.[69] Triphenylphosphine (2.885 g, 11.0 mmol) and 1-bromo-2-(bromomethyl)--benzene (2.975 g, 12.0 mmol) were stirred in THF (20 mL) at r.t. overnight. The solvent was evaporated, and the

resulting mixture was dissolved in diethyl ether (50 mL). Precipitated salt was filtered off and the filtrate was evaporated to afford 5.97 g (quant.) of (2-bromobenzyl)triphenylphosphonium bromide, which was dissolved in THF (140 mL) and stirred with sodium hydride (0.555 g, 60% in mineral oil dispersion, 24.0 mmol) at 0 °C for 30 min. A solution of 3,4-dimethoxybenzaldehyde (2.097 g, 12.6 mmol) in THF (15 mL) was transferred by cannula to the reaction. The reaction mixture was stirred at r.t. overnight, quenched with saturated NH_4Cl solution (20 mL). The solution was transferred to the separatory funnel, extracted with hexane (2 x 200 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude was dissolved in benzene (60 mL) and diphenyl diselenide (0.062 g, 0.392 mmol) was added. The mixture was stirred at r.t for 2 days under ambient light. Evaporation of benzene, purification by column chromatography (SiO_2, gradient hexane/EA 20:1 to pure EA) and crystallization from a mixture of heptane and EA (10:1) yielded 2.49 g (61%) of **4b** as a colourless crystals; **R*f*** = 0.58 (3:1, hexane/EA); **M.p.** = 101-103 °C; **IR ν [cm^{-1}]:** 3052 (w), 2998 (w), 2932 (w), 2833 (w), 1599 (w), 1582 (w), 1509 (vs), 1463 (m), 1437 (m), 1418 (m), 1305 (s), 1265 (s), 1246 (s), 1235 (m), 1156 (m), 1137 (vs), 1020 (vs), 956 (s), 799 (m), 743 (s), 667 (m), 550 (m); **MS EI+ *m/z*, (%):** 320/318 (100, $[M]^{+\bullet}$), 305/303 (11, $[M–CH_3]^+$), 239 (55, $[M–Br]^+$), 224 (56, $[M–Br–CH_3]^{+\bullet}$), 208 (53, $[M–Br–CH_3O]^{+\bullet}$), 196 (30, $[M–Br–CH_3–C_2H_4]^+$), 181 (35, $[M–Br–CH_3O–CO]^+$), 165 (38, $[M–Br–CH_3–CO–CH_3O]^+$), 152 (45); **HRMS EI+ *m/z*:** $[M(^{79}Br)]^{+\bullet}$ Calcd.: 318.0255; Found: 318.0254; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.65 (dd, *J* = 7.8, 1.6 Hz, 1H, CH-5), 7.58 (dd, *J* = 8.1, 1.2 Hz, 1H, CH-2), 7.32 (d, *J* = 16.3 Hz, 1H, CH-7), 7.30 (td, *J* = 7.6, 0.8 Hz, 1H, CH-3), 7.12-7.08 (m, 3H, CH-4, CH-10, CH-14), 6.99 (d, *J* = 16.1 Hz, 1H, CH-8), 6.88 (d, *J* = 8.8 Hz, 1H, CH-13), 3.96 (s, 3H, 11-OCH_3), 3.91 (s, 3H, 12-OCH_3); **^{13}C NMR (100-MHz, $CDCl_3$):** δ = 149.4 (s, C-12), 149.3 (s, C-11), 137.4 (s, C-6), 133.2 (d, C-2), 131.4 (d, C-8), 130.3 (s, C-9), 128.6 (d, C-4), 127.7 (d, C-3), 126.7 (d, C-5), 125.7 (d, C-7), 124.1 (s, C-1), 120.4 (d, C-14), 111.4 (d, C-13), 109.3 (d, C-10), 56.11 (q, 12-OCH_3), 56.06 (q, 11-OCH_3).

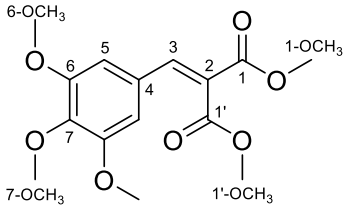
***(E)*-2-Bromo-1-(3,4-dimethoxystyryl)-3,5-dimethoxybenzene (4c):**



A solution of 3,4-dimehoxybenzaldehyde (5 g, 30.1 mmol) in methanol (50 mL) was stirred at 0 °C, $NaBH_4$ (1.14 g, 30.2 mmol) was added in 3 portions after 20 min. The mixture was stirred at r.t. for 2 h, the solvent was evaporated, and the crude product was dissolved in diethyl ether (50 mL). The solution was cooled to 0 °C and PBr_3 (5.1 mL, 57 mmol) was added dropwise. After 5 h, the reaction was quenched by cold water (50 mL). The solution was transferred to the separatory funnel, extracted with DCM (3 x 150 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated, THF (80 mL) and triphenylphosphine (8.5 g, 32.4 mmol) were added and the mixture was stirred at r.t. overnight. After evaporation of the solvent, the crude product was suspended in pentane (50 mL) and filtered to get 12.1 g (81%) of 3,4-dimethoxybenzyltriphenylphosphonium bromide as a white solid after drying in vacuum. The phosphonium bromide (9.09 g, 18.5 mmol) was dissolved in THF (150 mL) and treated with *n*-butyllithium (11.8 mL, 18.8 mmol) at 0 °C for 30 min. 2-Bromo-3,5-dimethoxybenzaldehyde (4.29 g, 17.6 mmol) was prepared according to the literature in 92% yield,[70] was added by cannula in THF (25 ml) to the reaction. The mixture was stirred at r.t. for 2 h. The reaction was cooled to 0 °C, quenched by saturated NH_4Cl solution (50 mL). The solution was transferred to the separatory funnel, extracted with EA (2 x 100 mL) and the combined organic layers were dried over Na_2SO_4. The crude product was dissolved in benzene (50 mL) and stirred with diphenyl diselenide (0.300 g, 0.961 mmol) by irradiation with a halogen lamp at r.t. for 2 days. The purification of the residue by column chromatography (SiO_2, gradient hexane/EA 7:1 to pure EA) and repeated crystallization from EA gave 5.8 g of **4c** (88%); $\mathbf{R_f}$ = 0.62 (3:1, hexane/EA); **M.p.** = 105-107 °C; **IR ν [cm^{-1}]:** 3000 (w), 2936 (w), 2836 (w), 1582 (s), 1513 (s), 1451 (m), 1416 (m), 1331 (m), 1265 (s), 1232 (s), 1202 (m), 1160 (s), 1139 (m), 1081 (s), 1022 (s), 959 (w), 825 (w), 802 (w); **MS ESI+ m/z, (%):** 403/401 (100, $[M+Na]^+$), 381/379 (40, $[M+H]^+$), 300 (25, $[M-Br+H]^+$); **HRMS ESI+ m/z:** $[M+Na]^+$ Calcd. for $C_{18}H_{19}O_4BrNa$: 401.0359; Found: 403.0360; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.39 (d, *J* = 16.1 Hz, 1H, CH-7), 7.11-7.08 (m, 2H, CH-3, CH-10, CH-14), 6.96 (d, *J* = 16.1 Hz,

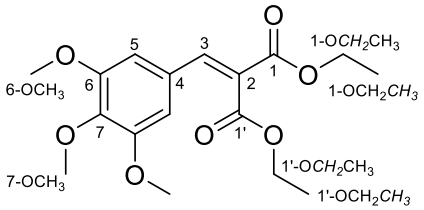
1H, CH-8), 6.87 (d, *J* = 8.8 Hz, 1H, CH-13), 6.80 (d, *J* = 2.7 Hz, 1H, CH-5), 6.42 (d, *J* = 2.7 Hz, 1H, CH-3), 3.95 (s, 3H, 11-OCH_3), 3.91 (s, 3H, 12-OCH_3), 3.88 (s, 3H, 2-OCH_3), 3.86 (s, 3H, 4-OCH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 159.7 (s, C-4), 157.0 (s, C-2), 149.5 (s, C-12), 149.3 (s, C-11), 139.0 (s, C-6), 131.6 (d, C-8), 130.2 (s, C-9), 126.2 (d, C-7), 120.5 (d, C-14), 111.3 (d, C-13), 109.2 (d, C-10), 105.1 (s, C-1), 102.6 (d, C-5), 99.0 (d, C-3), 56.5 (q, 4-OCH_3), 56.11 (q, 2-OCH_3), 56.06 (q, 11-OCH_3/12-OCH_3), 55.7 (q, 11-OCH_3/12-OCH_3).

Dimethyl 2-(3,4,5-trimethoxybenzylidene)malonate (8b):



The compound was prepared according to the published synthesis of dimethyl 2-benzylidenemalonate with some modifications.[71] Dimethyl malonate (3.9 mL, 33.9 mmol) and 3,4,5-trimethoxybenzalehyde (5 g, 25.5 mmol) were dissolved in toluene (25 mL). Piperidine (0.225 mL, 2.29 mmol) and acetic acid (0.150 mL, 2.55 mmol) were added and the mixture was stirred at 140 °C using a Dean-Stark apparatus. Evaporation of the solvent and purification of the residue by flash column chromatography (SiO_2, gradient hexane/EA 11:1 to pure EA) yielded 4.95 g (62%) of **8b** as colourless crystals; **R_f** = 0.22 (3:1, hexane/EA); **M.p.** = 69-71 °C; **IR ν [cm^{-1}]:** 2951 (w), 2841 (w), 1724 (m), 1623 (s), 1580 (w), 1506 (m), 1434 (m), 1419 (m), 1374 (w), 1334 (w), 1245 (s), 1214 (s), 1153 (m), 1122 (vs), 1067 (s), 998 (m), 933 (w), 832 (w), 623 (w); **MS ESI+ *m/z*, (%):** 643 (4, $[2M+Na]^+$), 333 (100, $[M+Na]^+$), 279 (7, $[M+H–MeOH]^+$); **HRMS ESI+ m/z:** $[M+Na]^+$ Calcd. for $C_{15}H_{18}O_7Na$: 333.0945; Found: 334.0945; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.67 (s, 1H, CH-3), 6.70 (s, 2H, CH-5), 3.87 (s, 3H, 7-OCH_3), 3.85 (s, 3H, 1-OCH_3/1'-OCH_3), 3.84 (s, 9H, 1-OCH_3/1'-OCH_3, 6-OCH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 167.5 (s, C-1/C-1'), 164.6 (s, C-1/C-1'), 153.4 (s, C-6), 142.8 (d, C-3), 140.5 (s, C-7), 128.1 (s, C-4), 124.7 (s, C-2), 106.9 (d, C-5), 61.1 (q, 7-OCH_3), 56.2 (q, 6-OCH_3), 52.83 (q, 1-OCH_3/1'-OCH_3), 52.80 (q, 1-OCH_3/1'-OCH_3).

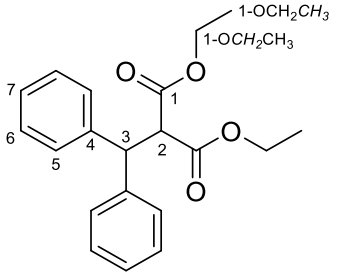
Diethyl 2-(3,4,5-trimethoxybenzylidene)malonate (8c):



The compound was prepared according to a published synthesis of the 3,4-dimethoxylated analogue with some modifications.[72] 3,4,5-Trimethoxybenzaldehyde (4.706 g, 24.0 mmol) and diethyl malonate (3.8 mL, 25.0 mmol) were used as starting materials and dissolved in benzene (20 mL). Piperidine (0.4 mL, 4.03 mmol) and benzoic acid (0.320 g, 2.62 mmol) were added and the mixture was stirred with a Dean-Stark trap at 80 °C. Evaporation of the solvent and purification of the residue by three cycles of crystallizations from heptane/EA (10:1) gave 5.5 g (67%) of **8c** as colourless crystals; $\mathbf{R_f}$ = 0.63 (3:1, hexane/EA); **M.p.** = 70-72 °C; **IR ν [cm^{-1}]:** 2981 (w), 2940 (w), 2840 (w), 1721 (s), 1626 (m), 1580 (m), 1506 (m), 1455 (m), 1421 (m), 1378 (m), 1333 (m), 1239 (s), 1211 (s), 1154 (m), 1124 (vs), 1065 (m), 1003 (m), 861 (w), 839 (w), 641 (w), 622 (w); **MS ESI+ m/z, (%):** 361 (100, $[M+Na]^+$), 289 (15); **HRMS ESI+ m/z:** $[M+Na]^+$ Calcd. for $C_{17}H_{22}O_7Na$: 361.1258; Found: 361.1258; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.64 (s, 1H, CH-3), 6.74 (s, 2H, CH-5), 4.36-4.28 (m, 4H, 1-O*CH*$_2$CH$_3$, 1‘-O*CH*$_2$CH$_3$), 3.88 (s, 3H, 7-OCH$_3$), 3.85 (s, 6H, 6-OCH$_3$), 1.35-1.30 (m, 6H, 1-OCH$_2$*CH*$_3$, 1‘-OCH$_2$*CH*$_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 167.1 (s, C-1/C-1‘), 164.3 (s, C-1/C-1‘), 153.4 (s, C-6), 142.1 (d, C-3), 140.4 (s, C-7), 128.4 (s, C-4), 125.6 (s, C-2), 107.0 (d, C-5), 61.9 (t, 1-O*CH*$_2$CH$_3$/1‘-O*CH*$_2$CH$_3$), 61.8 (t, 1-O*CH*$_2$CH$_3$/1‘-O*CH*$_2$CH$_3$), 61.1 (q, 7-OCH$_3$), 56.2 (q, 6-OCH$_3$), 14.3 (q, 1-OCH$_2$*CH*$_3$/1‘-OCH$_2$*CH*$_3$), 14.2 (q, 1-OCH$_2$*CH*$_3$/1‘-OCH$_2$*CH*$_3$).

5.2.2 Conjugate additions

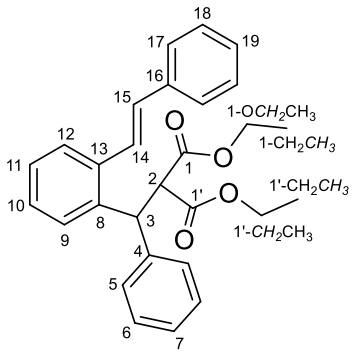
Diethyl 2-benzhydrylmalonate (17a):



Bromobenzene (61 µL, 0.579 mmol) was dissolved in THF (4 mL) and cooled to −78 °C. *tert*-Butyllithium (780 µL, 1.33 mmol, 1.7 M) was added and the mixture was stirred for 10 min. The dry ice-acetone bath was removed and CuBr·DMS (21 mg, 0.102 mmol) was added. The mixture was stirred at r.t. for 10 min and cooled to −40 °C. A solution of diethyl benzylidenemalonate (115 µL, 0.513 mmol) in THF (3 mL) was

added dropwise by cannula. The reaction was warmed to 0 °C over 1 h, quenched by saturated NH_4Cl solution (20 mL). The solution was transferred to the separatory funnel, extracted with DCM (3 x 100 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated and purification by column chromatography (SiO_2, gradient hexane/EA 15:1 to pure EA) yielded 125 mg (74%) of **17a**; $\mathbf{R_f}$ = 0.29 (30:20:1, hexane/DCM/diethyl ether); **IR ν [cm^{-1}]:** 3062 (w), 3029 (w), 2981 (w), 2937 (w), 1754 (m), 1727 (vs), 1630 (w), 1600 (w), 1495 (m), 1451 (m), 1368 (m), 1297 (m), 1259 (s), 1174 (s), 1153 (s), 1095 (m), 1060 (m), 1031 (s), 748 (m), 698 (vs), 605 (m); **MS ESI+ *m/z*, (%):** 707 (6, $[2M+Na+MeOH]^+$), 675 (16, $[2M+Na]^+$), 381 (20, $[M+Na+MeOH]^+$), 365 (12, $[M+K]^+$), 349 (100, $[M+Na]^+$); **HRMS ESI+ *m/z*:** $[M+Na]^+$ Calcd. for $C_{20}H_{22}O_4Na$: 349.1410; Found: 349.1411; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.32-7.24 (m, 8H, CH-5, CH-6), 7.17 (tt, *J* = 7.1, 1.5 Hz, 2H, CH-7), 4.76 (d, *J* = 12.2 Hz, 1H, CH-3), 4.33 (d, *J* = 12.2 Hz, 1H, CH-2), 4.01 (q, *J* = 7.1 Hz, 4H, 1-O*CH*$_2$CH$_3$), 1.02 (t, *J* = 7.1 Hz, 6H, 1-OCH$_2$*CH*$_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 167.8 (s, C-1), 141.5 (s, C-4), 128.7 (d, C-6), 127.9 (d, C-5), 127.0 (d, C-7), 61.6 (t, 1-O*CH*$_2$CH$_3$), 57.6 (d, C-2), 51.3 (d, C-3), 13.9 (q, 1-OCH$_2$*CH*$_3$).

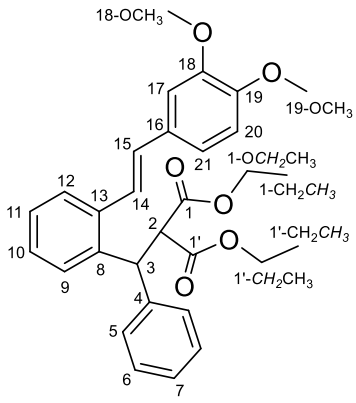
Diethyl (*E*)-3-(phenyl(3-styrylphenyl)methyl)malonate (17b):



(*E*)-1-Bromo-2-styrylbenzene (**4a**) (207 mg, 0.799 mmol) was dissolved in THF (5 mL) and cooled to −78 °C. *tert*-Butyllithium (1.0 mL, 1.71 mmol, 1.7 M) was added and the mixture was stirred 10 min. The dry ice-acetone bath was removed, the mixture was stirred at r.t. for 10 min, was cooled to −40 °C and CuBr·DMS (21 mg, 0.102 mmol) was added. A solution of diethyl benzylidenemalonate (115 µL, 0.513 mmol) in THF (8 mL) was added dropwise by cannula. The reaction was warmed to 0 °C over 2 h and quenched by saturated NH_4Cl solution (20 mL). The solution was transferred to the separatory funnel, extracted with DCM (3 x 100 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated and purification by column chromatography (SiO_2, gradient hexane/EA 10:1 to pure EA) gave 153 mg (70%) of **17b**; $\mathbf{R_f}$ = 0.40 (11:1, hexanes/EA); **IR ν [cm^{-1}]:** 3060 (w), 3027 (w), 2980 (w), 2934 (w), 1753 (s), 1727 (vs), 1598 (w), 1495 (m), 1449 (m), 1368 (m), 1301 (m), 1255 (s), 1174 (s), 1141 (s), 1096

(m), 1031 (s), 963 (m), 759 (s), 694 (s); **MS ESI+ *m/z*, (%):** 879 (10, $[2M+Na]^+$), 488 (40), 451 (100, $[M+Na]^+$); **HRMS ESI+ m/z:** $[M+Na]^+$ Calcd. for $C_{28}H_{28}O_4Na$: 451.1880; Found: 452.1880; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.65 (d, *J* = 16.0 Hz, 1H, CH-14), 7.52-7.50 (m, 3H, CH-5, CH-12), 7.43-7.39 (m, 3H, CH-6, CH-9), 7.31-7.18 (m, 7H, CH-10, CH-11, CH-17, CH-18, CH-19), 7.17 (tt, *J* = 7.3, 2.3 Hz, 1H, CH-7), 6.90 (d, *J* = 16.0 Hz, 1H, CH-15), 5.23 (d, *J* = 12.1 Hz, 1H, CH-3), 4.42 (d, *J* = 12.1, 1H, CH-2), 4.06-4.00 (m, 4H, 1-OCH_2*CH_3*, 1'-OCH_2*CH_3*), 1.04 (t, *J* = 7.1 Hz, 3H, 1-OCH_2*CH_3*/1'-OCH_2*CH_3*), 1.03 (t, *J* = 7.1 Hz, 3H, 1-OCH_2*CH_3*/1'-OCH_2*CH_3*); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 168.0 (s, C-1/C-1'), 167.6 (s, C-1/C-1'), 140.8 (s, C-4), 139.0 (s, C-8), 137.7 (s, C-16), 137.2 (s, C-13), 131.7 (d, C-14), 128.8 (d, C-17/C-18), 128.7 (d, C-17/C-18), 128.3 (d, C-6), 127.84 (d, C-10/C-11/C-19), 127.81 (d, C-10/C-11/C-19), 127.3 (d, C-10/C-11/C-19), 127.2 (d, C-12), 127.0 (d, C-7), 126.8 (d, C-5), 126.6 (d, C-15), 126.4 (d, C-9), 61.7 (t, 1-O*CH_2*CH_3, 1'-O*CH_2*CH_3), 57.9 (d, C-2), 46.5 (d, C-3), 13.90 (q, 1-OCH_2*CH_3*/1'-OCH_2*CH_3*), 13.87 (q, 1-OCH_2*CH_3*/1'-OCH_2*CH_3*).

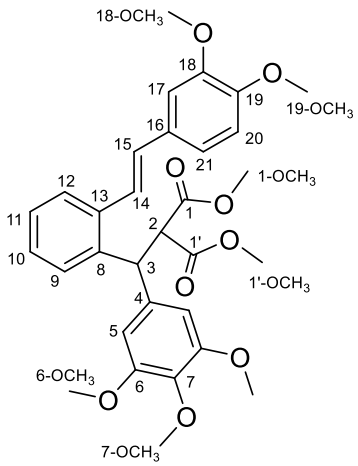
Diethyl (*E*)-3-((3-(18,19-dimethoxystyryl)phenyl)(phenyl)methyl)malonate (17c):



A solution of **4b** (208 mg, 0.652 mmol) in THF (8 mL) was cooled to −78 °C and *tert*-butyllithium (380 µL, 0.645 mmol, 1.7 M) was added. After 15 min, CuBr·DMS (21 mg, 0.102 mmol) was added and the mixture was stirred for 5 min. A solution of diethyl benzylidenemalonate (115 µL, 0.513 mmol) in THF (8 mL) was added dropwise. The reaction was warmed to 0 °C over 2 h and quenched by saturated NH_4Cl solution (20 mL). The solution was transferred to the separatory funnel, extracted with diethyl ether (3 x 100 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated and purification by column chromatography (SiO_2, gradient hexane/EA 10:1 to pure EA) afforded 247 mg (98%) of **17c**; **R_f** = 0.28 (3:1, hexane/EA); **IR *ν* [cm^{-1}]:** 2990 (w), 2846 (w), 1758 (m), 1734 (m), 1606 (w), 1588 (w), 1518 (s), 1469 (w), 1307 (w), 1264 (s), 1180 (m), 1160 (m), 1141 (s), 1028 (s), 910 (s), 805 (w), 728 (vs), 701 (s), 649 (m); **MS ESI+ *m/z*, (%):** 999 (30, $[2M+Na]^+$), 527 (35, $[M+K]^+$), 511 (100, $[M+Na]^+$), 329 (15, $[M+H–CH_2(COOEt)_2]^+$); **HRMS ESI+ *m/z*:**

[M+Na]$^+$ Calcd. for $C_{30}H_{32}O_6Na$: 511.2091; Found: 511.2089; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.49 (d, *J* = 7.4 Hz, 1H, CH-12), 7.41 (d, *J* = 16.0 Hz, 1H, CH-14), 7.37 (d, *J* = 7.6 Hz, 1H, CH-9), 7.28-7.20 (m, 6H, CH-5, CH-6, CH-10, CH-11), 7.18-7.13 (m, 1H, CH-7), 7.04 (d, *J* = 7.7 Hz, 1H, CH-21), 7.03 (s, 1H, CH-17), 6.87 (d, *J* = 7.9 Hz, 1H, CH-20), 6.80 (d, *J* = 15.9 Hz, 1H, CH-15), 5.17 (d, *J* = 13.3 Hz, 1H, CH-3), 4.36 (d, *J* = 13.5 Hz, 1H, CH-2), 4.04-3.97 (m, 4H, 1-O*CH*$_2$CH$_3$, 1'-O*CH*$_2$CH$_3$), 3.96 (s, 3H, 18-OCH$_3$), 3.92 (s, 3H, 19-OCH$_3$), 1.01 (t, *J* = 7.1 Hz, 3H, 1-OCH$_2$*CH*$_3$/1'-OCH$_2$*CH*$_3$), 1.00 (t, *J* = 7.1 Hz, 3H, 1-OCH$_2$*CH*$_3$/1'-OCH$_2$*CH*$_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 168.1 (s, C-1/C-1'), 167.7 (s, C-1/C-1'), 149.2 (s, C-18/C-19), 149.1 (s, C-18/C-19), 140.9 (s, C-4), 138.7 (s, C-8), 137.4 (s, C-13), 131.2 (d, C-15), 130.9 (s, C-16), 128.6 (d, C-6), 128.4 (d, C-5), 127.5 (d, 11), 127.2 (d, C-7/C-10), 127.1 (d, C-12), 127.0 (d, C-7/C-10), 126.3 (d, C-9), 124.8 (d, C-14), 120.1 (d, C-21), 111.3 (d, C-20), 109.1 (d, C-17), 61.7 (t, 1-O*CH*$_2$CH$_3$, 1'-O*CH*$_2$CH$_3$), 57.9 (d, C-2), 56.1 (q, 19-OCH$_3$), 56.0 (q, 18-OCH$_3$), 46.7 (d, C-3), 13.92 (q, 1-OCH$_2$*CH*$_3$/1'-OCH$_2$*CH*$_3$), 13.91 (q, 1-OCH$_2$*CH*$_3$/1'-OCH$_2$*CH*$_3$).

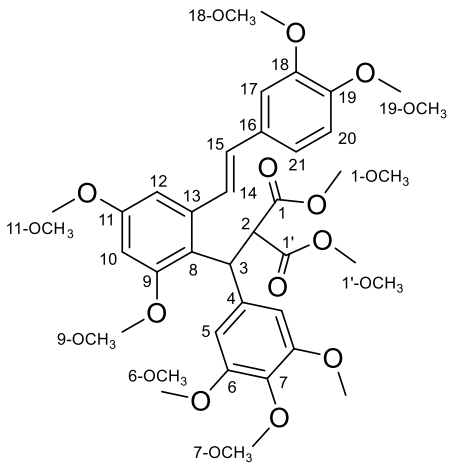
Dimethyl (*E*)-2-((2-(3,4-dimethoxystyryl)phenyl)(3,4,5-trimethoxyphenyl)methyl)-malonate (17d):



The compound was prepared according to procedure for synthesis of compound **17c** except for addition of Cu(I), which was added to the reaction mixture as a solution of CuBr·DMS (13 mg, 0.063 mmol) and LiBr (60 mg, 0.181 mg) in THF (3 mL). The compound **8b** (93 mg, 0.300 mmol) was added as starting material. The procedure yielded 162 mg (98%) of **17d**; **R$_f$** = 0.56 (2:1, hexanes/EA); **IR *ν* [cm^{-1}]:** 2999 (w), 2953 (w), 2836 (w), 1736 (m), 1588 (m), 1511 (m), 1456 (s), 1420 (m), 1248 (s), 1124 (vs), 1024 (s); **MS ESI+ *m/z*, (%):** 610 (34), 573 (100, [M+Na]$^+$); **HRMS ESI+ *m/z*,** [M+Na]$^+$ Calcd. for $C_{31}H_{34}O_9Na$: 573.2095; Found: 573.2091; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.49 (dd, *J* = 7.3, 1.8 Hz, 1H, CH-12), 7.41 (d, *J* = 16.0 Hz, 1H, CH-14), 7.31 (dd, *J* = 7.6, 1.6 Hz, 1H, CH-9), 7.28-7.20 (m, 2H, CH-10, CH-11), 7.06 (dd, *J* = 8.4, 1.9 Hz, 1H, CH-21), 7.01 (d, *J* = 2.0 Hz, 1H, CH-17), 6.87 (d, *J* = 8.2 Hz, 1H, CH-20), 6.79 (d, *J* = 16.0 Hz, 1H, CH-15), 6.44 (s, 2H,

CH-5), 5.11 (d, *J* = 12.0 Hz, 1H, CH-3), 4.39 (d, *J* = 12.0 Hz, 1H, CH-2), 3.94 (s, 3H, 18-OCH_3/19-OCH_3), 3.92 (s, 3H, 18-OCH_3/19-OCH_3), 3.76 (s, 3H, 7-OCH_3), 3.71 (s, 6H, 6-OCH_3), 3.59 (s, 3H, 1-OCH_3), 3.57 (s, 3H, 1'-OCH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 168.5 (s, C-1), 168.0 (s, C-1'), 153.2 (s, C-6), 149.3 (s, C-18/C-19), 149.2 (s, C-18/C-19), 138.5 (s, C-8), 137.6 (s, C-13), 137.0 (s, C-7), 136.4 (s, C-4), 131.7 (d, C-15), 130.9 (s, C-16), 127.7 (d, C-10/C-11/C-12), 127.5 (d, C-10/C-11/C-12), 127.4 (d, C-10/C-11/C-12), 125.8 (d, C-9), 125.2 (d, C-14), 119.8 (d, C-21), 111.4 (d, C-20), 109.6 (d, C-17), 105.5 (d, C-5), 60.9 (q, 7-OCH_3), 57.4 (d, C-2), 56.15 (q, 6-OCH_3, 18-OCH_3, 19-OCH_3), 52.9 (q, 1-OCH_3, 1'-OCH_3), 46.8 (d, C-3).

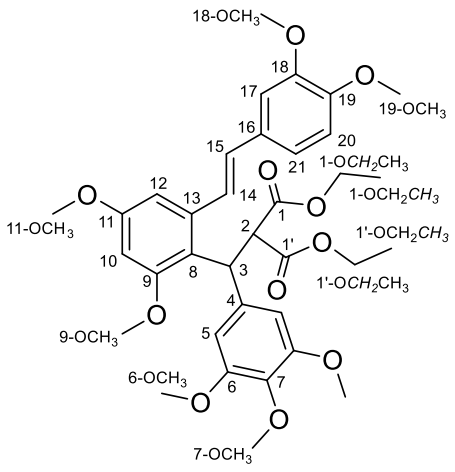
Dimethyl (*E*)-2-((2-(3,4-dimethoxystyryl)-4,6-dimethoxyphenyl)(3,4,5-trimethoxyphenyl)methyl)malonate (17e):



A solution of **4c** (100 mg, 0.265 mmol) in THF (7 mL) was cooled to −78 °C. *tert*-Butyllithium (155 µl, 0.264 mmol) was added. After 15 min, a solution of CuBr·DMS (9 mg, 0.041 mmol) and LiBr (41 mg, 0.124 mmol) in THF (3 mL) was added and the mixture was stirred for 5 min. Solution of **8b** (64 mg, 0.206 mmol) in THF (3 mL) was added dropwise. The reaction slowly warmed to r.t. After 24 h, the mixture was quenched by saturated NH_4Cl solution (15 ml). The solution was transferred to the separatory funnel, extracted with diethyl ether (3 x 100 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated and purification by column chromatography (SiO_2, gradeint hexane/EA 10:1 to pure EA) gave 64 mg (51%) of **17e**; **R_f** = 0.23 (1:1, hexanes/EA); **IR ν [cm^{-1}]:** 2998 (w), 2952 (w), 2837 (w), 1737 (m), 1589 (m), 1511 (s), 1457 (m), 1420 (m), 1323 (m), 1260 (s), 1231 (s), 1199 (m), 1125 (vs), 1025 (m), 964 (w), 849 (w), 807 (w); **MS ESI+ m/z, (%):** 633 (100, $[M+Na]^+$), 479 (23, $[M+H–CH_2(COOCH_3)_2]^+$), 311 (13, $[M+H–(CH)_2Ph_2(OMe)_4]^+$); **HRMS ESI+ m/z:** $[M+Na]^+$ Calcd. for $C_{33}H_{38}O_{11}Na$: 633.2306; Found: 633.2307; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.57 (br d, *J* = 15.5 Hz, 1H, CH-14), 7.10 (d, *J* = 8.3 Hz, 1H, H-21), 7.06 (s, 1H, CH-17), 6.88 (d, *J* = 8.3 Hz, 1H, CH-20), 6.81 (d, *J* = 15.9 Hz, 1H, CH-15), 6.60 (d, *J* = 2.5 Hz, 1H, CH-12), 6.54 (s,

2H, CH-5), 6.36 (d, *J* = 2.5 Hz, 1H, CH-10), 5.19 (br d, *J* = 10.7 Hz, 1H, CH-3), 4.85 (br d, *J* = 10.9 Hz, 1H, CH-2), 3.94 (s, 3H, 18-OCH_3), 3.91 (s, 3H, 19-OCH_3), 3.80 (s, 3H, 11-OCH_3), 3.77 (s, 3H, 9-OCH_3), 3.75 (s, 3H, 7-OCH_3), 3.69 (s, 6H, 6-OMe), 3.65 (s, 3H, 1-OCH_3/1‘-OCH_3), 3.50 (s, 3H, 1-OCH_3/1‘-OCH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 169.3 (s, C-1/C-1‘), 168.6 (s, C-1/C-1‘), 159.4 (s, C-11), 158.9 (s, C-9), 152.7 (s, C-6), 149.24 (s, C-18), 149.19 (s, C-19), 140.2 (s, C-13), 137.1 (s, C-4), 136.4 (s, C-7), 132.5 (d, C-15), 130.6 (s, C-16), 126.7 (d, C-14), 120.0 (s, C-8), 119.8 (d, C-21), 111.4 (d, C-20), 109.6 (d, C-17), 105.2 (d, C-5), 104.2 (d, C-12), 98.8 (d, C-10), 60.8 (q, 7-OCH_3), 56.09 (q, 19-OCH_3), 56.05 (q, 18-OCH_3), 55.9 (q, 6-OCH_3), 55.5 (d, C-2), 55.4 (q, 9-OCH_3), 54.6 (q, 11-OCH_3), 52.7 (1-OCH_3/1‘-OCH_3), 52.5 (q, 1-OCH_3/1‘-OCH_3), 43.9 (d, C-3).

Diethyl (*E*)-2-((2-(3,4-dimethoxystyryl)-4,6-dimethoxyphenyl)(3,4,5-trimethoxyphenyl)methyl)malonate (17f):

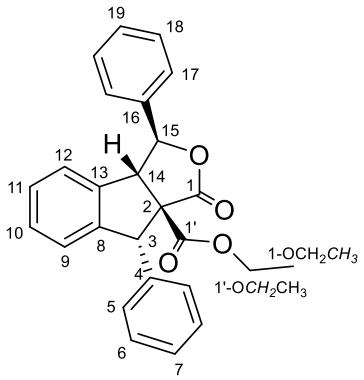


The compound **17f** (74 mg, 98%) was prepared according to procedure for synthesis of compound **17e** except for ratio of reagents. Compound **4c** (89 mg, 0.237 mmol), *tert*-butyllithium (140 µl, 0.237 mmol, 1.7 M) and **8c** (40 mg, 0.118 mmol) reacted in the ratio 2:2:1. In this experiment the reaction was quenched at −40 °C after 2 h; **R_f** = 0.44 (1:1, hexanes/EA); **IR ν [cm^{-1}]:** 2937 (w), 2836 (w), 1751 (m), 1731 (m), 1589 (m), 1511 (m), 1461 (m), 1420 (m), 1323 (m), 1258 (s), 1230 (s), 1200 (m), 1126 (vs), 1026 (m), 964 (w), 848 (w), 805 (w); **MS ESI+ m/z, (%):** 661 (100, $[M+Na]^+$), 479 (34, $[M+H–CH_2(COOCH_2CH_3)_2]^+$), 339 (24, $[M+H–(CH)_2Ph_2(OCH_3)_4]^+$); **HRMS ESI+ m/z:** $[M+Na]^+$ Calcd. for $C_{35}H_{42}O_{11}Na$: 661.2619; Found: 661.2619; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.62 (br d, *J* = 16.0 Hz, 1H, CH-14), 7.13 (d, *J* = 8.2 Hz, 1H, CH-21), 7.10 (s, 1H, CH-17), 6.91 (d, *J* = 8.2 Hz, 1H, CH-20), 6.83 (d, *J* = 15.9 Hz, 1H, CH-15), 6.62 (d, *J* = 2.5 Hz, 1H, CH-12), 6.60 (s, 2H, CH-5), 6.39 (d, *J* = 2.5 Hz, 1H, CH-10), 5.20 (br d, *J* = 10.7 Hz, 1H, CH-3), 4.96 (br d, *J* = 11.1 Hz, 1H, CH-2), 4.11-3.97 (m, 4H, 1-O*CH*$_2$CH$_3$, 1‘-O*CH*$_2$CH$_3$), 3.97 (s, 3H, 18-OCH_3), 3.95 (s, 3H, 19-OCH_3), 3.83 (s, 3H, 11-OCH_3), 3.82 (s, 3H, 9-OCH_3), 3.77

(s, 3H, 7-OCH_3), 3.72 (s, 6H, 6-OCH_3), 1.16 (t, J = 7.1 Hz, 3H, 1-OCH_2CH_3/1‘-OCH_2CH_3), 1.04 (t, J = 7.1 Hz, 3H, 1-OCH_2CH_3/1‘-OCH_2CH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 168.9 (s, C-1/C-1‘), 168.3 (s, C-1/C-1‘), 159.5 (s, C-11), 159.0 (s, C-9), 152.7 (s, C-6), 149.3 (s, C-19), 149.2 (s, C-18), 140.3 (s, C-13), 137.3 (s, C-4), 136.4 (s, C-7), 132.5 (d, C-15), 130.7 (s, C-16), 126.9 (d, C-14), 120.2 (s, C-8), 119.8 (d, C-21), 111.4 (d, C-20), 109.5 (d, C-17), 105.1 (d, C-5), 104.2 (d, C-12), 98.8 (d, C-10), 61.6 (t, 1-O$CH_2$$CH_3$/1‘-O$CH_2$$CH_3$), 61.4 (t, 1-O$CH_2$$CH_3$/1‘-O$CH_2$$CH_3$‘), 60.9 (q, 7-$OCH_3$), 56.14 (q, 9-$OCH_3$), 56.08 (q, 11-$OCH_3$), 56.0 (q, 6-$OCH_3$), 55.5 (q, 19-$OCH_3$), 55.4 (q, 18-$OCH_3$), 54.9 (d, C-2), 43.7 (d, C-3), 14.1 (q, 1-OCH_2CH_3/1‘-OCH_2CH_3), 14.0 (q, 1-OCH_2CH_3/1‘-OCH_2CH_3).

5.2.3 Tandem conjugate addition/oxidative cyclization leading to stilbenolignan analogues

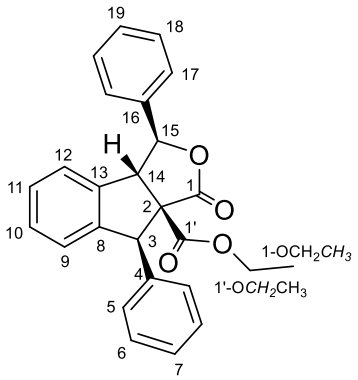
Ethyl (3S*,3aS*,8R*,8aR*)-1-oxo-3,8-diphenyl-3a,8-dihydro-1*H*-indeno[1,2-c]-furan-8a(3*H*)-carboxylate (26a):



(*E*)-1-Bromo-2-styrylbenzene (**4a**) (207 mg, 0.799 mmol) was dissolved in THF (5 mL) and cooled to −78 °C. *tert*-Butyllithium (1.0 mL, 1.71 mmol, 1.7 M) was added and the mixture was stirred 10 min. The dry ice-acetone bath was removed, the mixture was stirred at r.t. for 10 min, cooled to −40 °C and CuBr·DMS (21 mg, 0.102 mmol) was added. A solution of diethyl benzylidenemalonate (115 µL, 0.513 mmol) in THF (8 mL) was added dropwise by cannula. The mixture was warmed to 0 °C over 2 h and the solution of ferrocenium hexafluorophosphate (500 mg, 1.51 mmol) in 10 ml of THF was added from the ice bath dropwise by cannula over 10 min. After 1 h, the reaction was quenched by saturated NH_4Cl solution (25 mL). The solution was transferred to the separatory funnel, extracted with diethyl ether (3 x 100 mL). The organic extract was washed by 10% $Na_2S_2O_3$ solution (50 mL) and brine (50 mL) and the organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and purification by column chromatography (SiO_2, gradient hexane/EA 10:1 to pure EA) gave 53% of **26a** and 7% of ***diast*-26a**; R_f = 0.34 (5:1, hexane/EA); **M.p.** = 182-184 °C; **IR ν [cm^{-1}]:** 3029 (w),

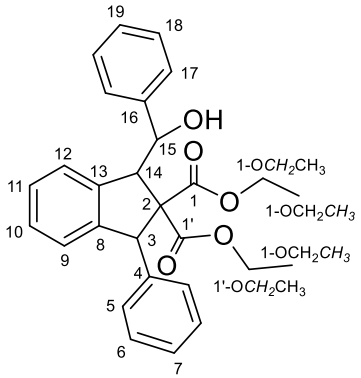
2923 (m), 2851 (w), 1775 (s), 1735 (s), 1495 (w), 1454 (m), 1228 (s), 1147 (s), 1019 (s), 755 (m), 729 (m), 697 (vs); **MS ESI+ m/z, (%):** 819 (5, $[2M+Na]^+$), 421 (100, $[M+Na]^+$), 399 (13, $[M+H]^+$); **HRMS ESI+ m/z:** $[M+Na^+]$: Calcd. for $C_{26}H_{22}O_4Na$: 421.1410; Found: 421.1410; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.50-7.12 (m, 14H, CH-5, CH-6, CH-7, CH-9, CH-10, CH-11, CH-12, CH-17, CH-18, CH-19), 5.61 (s, 1H, CH-3), 5.35 (d, *J* = 5.8 Hz, 1H, H-15), 4.50 (d, *J* = 5.8 Hz, 1H, H-14), 4.31-4.20 (m, 2H, 1‘-O*CH*$_2$CH$_3$), 1.26 (t, *J* = 7.1 Hz, 3H, 1‘-OCH$_2$*CH*$_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 171.7 (s, C-1), 169.9 (s, C-1‘), 143.7 (s, C-8), 141.2 (s, C-13), 139.5 (s, C-4/C-16), 139.4 (s, C-4/C-16), 129.6 (d, C-5), 129.2 (d, C_{Ar}), 129.1 (d, C-6/C-18), 128.9 (d, C_{Ar}), 128.7 (d, C-6/C-18), 128.6 (d, C_{Ar}), 127.9 (d, C_{Ar}), 126.6 (d, C_{Ar}), 125.9 (d, C-17), 123.9 (d, C-12), 86.1 (d, C-15), 67.7 (s, C-2), 63.0 (t, 1‘-O*CH*$_2$CH$_3$), 61.3 (d, C-14), 56.6 (d, C-3), 14.0 (q, 1‘-OCH$_2$*CH*$_3$). The relative configuration was determined by X-ray crystallographic analysis available in **Chapter 3.3**.

Ethyl (3S*,3aS*,8S*,8aR*)-1-oxo-3,8-diphenyl-3a,8-dihydro-1*H*-indeno[1,2-c]-furan-8a(3*H*)-carboxylate (*diast*-26a):



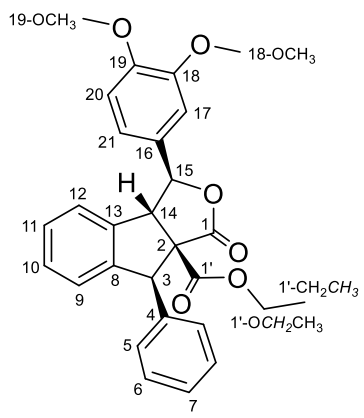
The compound ***diast*-26a** was prepared in 7% yield according to the procedure for synthesis of compound **26a**, which is described above and was isolated as a mixture with **26a**; $\mathbf{R}_f$ = 0.34 (5:1, hexane/EA); **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.59-6.95 (m, 14H, CH-5, CH-6, CH-7, CH-9, CH-10, CH-11, CH-12, CH-17, CH-18, CH-19), 5.80 (s, 1H, CH-15), 5.14 (s, 1H, CH-3), 4.75 (s, 1H, CH-14), 3.55-3.43 (m, 2H, 1‘-O*CH*$_2$CH$_3$), 0.68 (t, *J* = 7.1 Hz, 3H, 1‘-OCH$_2$*CH*$_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 174.8 (s, C-1), 165.9 (s, C-1‘), 143.4 (s, C-8), 141.2 (s, C-13), 139.7 (s, C-4/C-16), 139.1 (s, C-4/C-16), 129.5 (d, C_{Ar}), 129.0 (d, C_{Ar}), 128.9 (d, C_{Ar}), 128.8 (d, C_{Ar}), 128.34 (d, C_{Ar}), 128.33 (d, C_{Ar}), 127.7 (d, C_{Ar}), 126.13 (d, C_{Ar}), 126.10 (d, C_{Ar}), 124.6 (d, C_{Ar}), 84.7 (d, C-15), 66.1 (s, C-2), 62.0 (t, 1‘-O*CH*$_2$CH$_3$), 59.2 (d, C-3), 56.4 (d, C-14), 13.4 (q, 1‘-OCH$_2$*CH*$_3$). The relative configuration was assigned by comparison of the ^{1}H and ^{13}C NMR spectra with those of lactone **26d**, whose relative configuration was determined by X-ray crystallography analysis available in **Chapter 3.3**.

Diethyl 1-(hydroxy(phenyl)methyl)-3-phenyl-1,3-dihydro-2*H*-indene-2,2--dicarboxylate (27a):



The compound **27a** was prepared according to procedure for synthesis of compound **26a** and ***diast*-26a** except for addition of ferrocenium hexafluorophosphate (500 mg, 1.51 mmol), which was added directly into the temporarily opened flask with reaction mixture at 0 °C. The reaction yielded 19% of **26a**, 3% of ***diast*-26a** and 17% of **27a**; $\mathbf{R_f}$ = 0.30 (5:1, hexane/EA); **IR ν [cm^{-1}]:** 3031 (w), 2981 (w), 2928 (w), 1780 (w), 1724 (m), 1701 (w), 1454 (w), 1368 (w), 1263 (s), 1198 (m), 1078 (m), 1031 (m), 734 (vs), 669 (vs), 588 (m); **MS ESI+ m/z, (%):** 911 (22, $[2M+Na]^+$), 483 (18, $[M+K]^+$), 467 (100, $[M+Na]^+$), 421 (82, $[M+Na-EtOH]^+$), 375 (21, $[M+Na-2EtOH]^+$); **HRMS ESI+ m/z:** $[M+Na]^+$ Calcd. for $C_{28}H_{28}O_5Na$: 467.1829; Found: 467.1829; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = **7**.60 (d, *J* = 7.1 Hz, 2H, CH-17), 7.46 (t, *J* = 7.4 Hz, 2H, CH-18), 7.44-7.29 (m, 6H, CH-5, CH-6, CH-7, CH-9), 7.12 (t, *J* = 7.5 Hz, 1H, CH-10), 7.03 (t, *J* = 7.5 Hz, 1H, CH-11), 6.89 (d, *J* = 7.6 Hz, 1H, CH-9), 6.58 (d, *J* = 7.7 Hz, 1H, CH-12), 5.20 (s, 1H, CH-3), 5.09 (t, *J* = 9.7 Hz, 1H, CH-15), 4.71 (d, *J* = 10.0 Hz, 1H, 15-OH), 4.51-4.39 (m, 2H, 1-O*CH_2*CH_3/1‘-O*CH_2*CH_3), 4.42 (d, *J* = 9.7 Hz, 1H, CH-14), 3.81-3.73 (m, 2H, 1-O*CH_2*CH_3/1‘-O*CH_2*CH_3), 1.44 (t, *J* = 7.1 Hz, 3H, 1-OCH_2*CH_3*/1‘-OCH_2*CH_3*), 0.88 (t, *J* = 7.2 Hz, 3H, 1-OCH_2*CH_3*/1‘-OCH_2*CH_3*); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 174.9 (s, C-1/C-1‘), 168.0 (s, C-1/C-1‘), 144.7 (s, C-16), 143.1 (s, C-8), 141.7 (s, C-13), 138.6 (s, C-4), 131.4 (d, C-5), 129.1 (d, C-18), 128.2 (d, C-7/C-19), 127.9 (d, C-17), 127.72 (d, C-6), 127.68 (d, C-7/C-19), 127.4 (d, C-11), 127.2 (d, C-10), 124.9 (d, C-9), 123.7 (d, C-12), 75.0 (d, C-15), 70.8 (s, C-2), 62.9 (t, 1-O*CH_2*CH_3/1‘-O*CH_2*CH_3), 61.2 (t, 1-O*CH_2*CH_3/1‘-O*CH_2*CH_3), 57.3 (d, C-14), 56.5 (d, C-3), 14.2 (q, 1-OCH_2*CH_3*/1‘-OCH_2*CH_3*), 13.6 (q, 1-OCH_2*CH_3*/1‘-OCH_2*CH_3*).

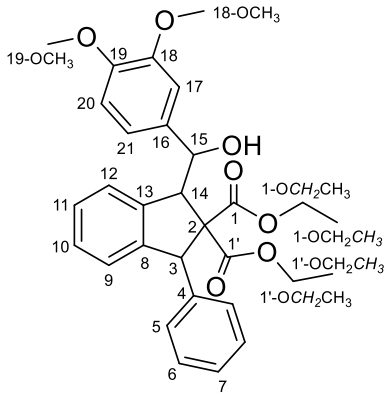
Ethyl (3S*,3aS*,8S*,8aR*)-3-(3,4-dimethoxyphenyl)-1-oxo-8-phenyl-3a,8-dihydro--1*H*-indeno[1,2-c]furan-8a(3*H*)-carboxylate (26b):



A solution of **4b** (208 mg, 0.652 mmol) in THF (8 mL) was cooled to −78 °C. *tert*-Butyllithium (380 µl, 0.645 mmol, 1.7 M) was added to the solution. After 15 min, CuBr·DMS (21 mg, 0.102 mmol) was added and stirring was continued for 5 min. A solution of diethyl benzylidenemalonate (115 µL, 0.513 mmol) in THF (8 mL) was added dropwise. The reaction slowly warmed to 0 °C over 2 h. Ferrocenium hexafluorophosphate (300 mg, 0.906 mmol) was added. After 30 min, the reaction was quenched by saturated NH_4Cl solution (15 mL). The solution was transferred to the separatory funnel and extracted with diethyl ether (3 x 100 mL). The organic extract was washed with 10% $Na_2S_2O_3$ solution (50 mL) and the organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and purification by column chromatography (SiO_2, gradient hexane/EA 10:1 to pure EA) afforded 10% of **17c**, 3% of **26b**, 8% of **27b** and 32% of **28b**; $\mathbf{R_f}$ = 0.32 (3:1, hexane/EA); **IR ν [cm^{-1}]:** 2930 (w), 2853 (w), 1782 (m), 1730 (m), 1595 (w), 1516 (s), 1454 (m), 1256 (s), 1238 (s), 1141 (vs), 1025 (s), 803 (m), 734 (vs), 699 (s); **MS ESI+ m/z, (%):** 939 (7, $[2M+Na]^+$), 527 (11, $[M+Na+CH_2CH_3OH]^+$), 518 (26), 481 (100, $[M+Na]^+$); **HRMS ESI+ m/z:** $[M+Na]^+$ Calcd. for $C_{28}H_{26}O_6Na$: 481.1622; Found: 481.1620; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.56 (d, *J* = 7.7 Hz, 1H, CH-12), 7.42 (t, *J* = 7.2 Hz, 1H, CH-11), 7.32 (t, *J* = 7.5 Hz, 1H, CH-10), 7.21-7.17 (m, 3H, CH-6, CH-7), 7.12 (d, *J* = 7.7 Hz, 1H, CH-9), 6.99-6.94 (m, 3H, CH-5, CH-21), 6.88-6.86 (m, 2H, CH-17, CH-20), 5.72 (s, 1H, CH-15), 5.14 (s, 1H, CH-3), 4.75 (s, 1H, CH-14), 3.89 (s, 3H, 18-OCH_3/19-OCH_3), 3.87 (s, 3H, 18-OCH_3/19-OCH_3), 3.53 (q, *J* = 7.1 Hz, 2H, 1'-O*CH*$_2$CH$_3$), 0.71 (t, *J* = 7.1 Hz, 3H, 1'-OCH$_2$*CH*$_3$); **^{13}C NMR (100-MHz, $CDCl_3$):** δ = 174.8 (s, C-1), 166.3 (s, C-1'), 149.4 (s, C-18/C-19), 149.1 (s, C-18/C-19), 143.3 (s, C-8), 141.3 (s, C-13), 139.8 (s, C-4), 131.5 (s, C-16), 129.5 (d, C-10), 129.1 (d, C-5), 128.9 (d, C-11), 128.4 (d, C-6), 127.7 (d, C-7), 126.1 (d, C-9), 124.0 (d, C-12), 117.5 (d, C-21), 111.3 (d, C-20), 108.1 (d, C-17), 85.1 (d, C-15), 66.3 (s, C-2), 62.1 (t, 1'-O*CH*$_2$CH$_3$), 59.4 (d, C-3), 56.1 (q, 18-OCH_3, 19-OCH_3), 56.0 (d, C-14), 13.5 (q, 1'-OCH$_2$*CH*$_3$). The relative configuration was assigned by comparison

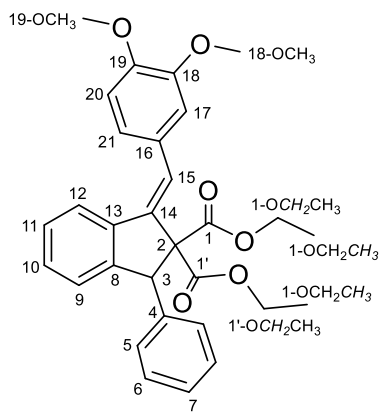
of the ^{1}H and ^{13}C NMR spectra with those of lactone **26d**, whose relative configuration was determined by X-ray crystallography analysis available in **Chapter 3.3**.

Diethyl 1-((3,4-dimethoxyphenyl)(hydroxy)methyl)-3-phenyl-1,3-dihydro-2*H*--indene-2,2-dicarboxylate (27b):



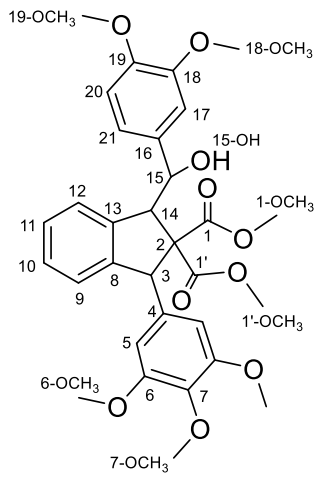
The compound **27b** with the highest yield was prepared according to procedure for synthesis of compound **26b** except for addition of ferrocenium hexafluorophosphate (300 mg, 0.906 mmol), which was added to the temporarily opened flask with reaction mixture in two portions after 5 min at 0 °C. After 30 min, the reaction was warmed to r.t. and stirred 1 h. After workup the reaction yielded 22% of **17c**, 31% of **27b** and 17% of **28b**; $\mathbf{R_f}$ = 0.30 (3:1, hexane/EA); **IR ν [cm^{-1}]:** 3061 (w), 3029 (w), 2981 (w), 2937 (w), 2836 (w), 1780 (m), 1734 (m), 1699 (m), 1515 (s), 1453 (m), 1262 (vs), 1238 (s), 1141 (s), 1026 (s), 751 (m), 702 (m); **MS ESI+ m/z, (%):** 1031 (14, $[2M+Na]^+$), 985 (4, $[2M+Na–EtOH]^+$), 564 (19), 527 (100, $[M+Na]^+$), 487 (31, $[M+H–H_2O]^+$); **HRMS ESI+ m/z:** $[M+Na]^+$ Calcd. for $C_{30}H_{32}O_7Na$: 527.2040; Found: 527.2041; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.42-7.40 (m, 2H, CH-5), 7.32-7.29 (m, 3H, CH-6, CH-7), 7.14-7.10 (m, 3H, CH-10, CH-17, CH-21), 7.03 (t, *J* = 7.5 Hz, 1H, CH-11), 6.94 (d, *J* = 8.6 Hz, 1H, CH-20), 6.88 (d, *J* = 7.7 Hz, 1H, CH-12), 6.56 (d, *J* = 7.6 Hz, 1H, CH-9), 5.20 (s, 1H, CH-3), 5.03 (br t, *J* = 9.6 Hz, 1H, CH-15), 4.59 (br d, *J* = 9.9 Hz, 1H, 15-OH), 4.48-4.38 (m, 3H, 1-O*CH*$_2$CH$_3$/1‘-O*CH*$_2$CH$_3$, CH-14), 3.94 (s, 3H, 18-OCH$_3$/19-OCH$_3$), 3.93 (s, 3H, 18-OMe/19-OMe), 3.82-3.69 (m, 2H, 1-O*CH*$_2$CH$_3$/1‘-O*CH*$_2$CH$_3$), 1.43 (t, *J* = 7.1 Hz, 3H, 1-OCH$_2$*CH*$_3$/1‘-OCH$_2$*CH*$_3$), 0.87 (t, *J* = 7.1 Hz, 3H, 1-OCH$_2$*CH*$_3$/1‘-OCH$_2$*CH*$_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 175.0 (s, C-1/C-1’), 168.0 (s, C-1/C-1’), 149.5 (s, C-18/C-19), 149.0 (s, C-18/C-19), 143.1 (s, C-8), 141.8 (s, C-13), 138.7 (s, C-4), 137.3 (s, C-16), 131.4 (d, C-5), 127.73 (d, C-6), 127.70 (d, C-7), 127.4 (d, C-10/C-11), 127.3 (d, C-10/C-11), 124.9 (d, C-12), 123.9 (d, C-9), 120.0 (d, C-21), 111.5 (d, C-20), 111.1 (d, C-17), 74.8 (d, C-15), 70.8 (s, C-2), 62.9 (t, 1-O*CH*$_2$CH$_3$/1‘-O*CH*$_2$CH$_3$), 61.2 (t, 1-O*CH*$_2$CH$_3$/1‘-O*CH*$_2$CH$_3$), 57.2 (d, C-14), 56.6 (d, C-3), 56.1 (q, 18-OCH$_3$, 19-OCH$_3$), 14.2 (q, 1-OCH$_2$*CH*$_3$/1‘-OCH$_2$*CH*$_3$), 13.6 (q, 1-OCH$_2$*CH*$_3$/1‘-OCH$_2$*CH*$_3$).

Diethyl 1-(3,4-dimethoxybenzylidene)-3-phenyl-1,3-dihydro-2H-indene-2,2--dicarboxylate (28b):



The compound **28b** was prepared in 32% yield according to the procedure for synthesis of compound **26b**, which is described above; $\mathbf{R_f}$ = 0.36 (3:1, hexane/EA); **IR ν [cm^{-1}]:** 3062 (w), 2978 (w), 2934 (w), 2905 (w), 2836 (w), 1730 (vs), 1601 (w), 1513 (s), 1464 (m), 1263 (s), 1235 (vs), 1204 (m), 1138 (m), 1094 (m), 1027 (s), 762 (m), 701 (m); **MS ESI+ m/z, (%):** 995 (17, $[2M+Na]^+$), 525 (12, $[M+K]^+$), 509 (100, $[M+Na]^+$), 487 (24, $[M+H]^+$), 469 (20, $[M+H-H_2O]^+$); **HRMS ESI+ m/z:** $[M+Na^+]$ Calcd. for $C_{30}H_{30}O_6Na$: 509.1935; Found: 509.1935; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.29 (d, *J* = 7.9 Hz, 1H, CH-12), 7.23 (d, *J* = 7.5 Hz, 2H, CH-5), 7.20 (tt, *J* = 6.7, 2.9 Hz, 1H, CH-7), 7.14-7.11 (m, 3H, CH-6, CH-10), 7.12 (s, 1H, CH-15), 7.04 (d, *J* = 7.7 Hz, 1H, CH-9), 7.03 (d, *J* = 8.1 Hz, 1H, CH-21), 7.00 (s, 1H, CH-17), 6.98 (t, *J* = 7.5 Hz, 1H, CH-11), 6.90 (d, *J* = 8.1 Hz, 1H, CH-20), 5.36 (s, 1H, CH-3), 4.32-4.23 (m, 2H, 1-O*CH*$_2$CH$_3$/1'-O*CH*$_2$CH$_3$), 3.94 (s, 3H, 18-OCH$_3$/19-OCH$_3$), 3.86 (s, 3H, 18-OCH$_3$/19-OCH$_3$), 3.75-3.48 (m, 2H, 1-O*CH*$_2$CH$_3$/1'-O*CH*$_2$CH$_3$), 1.29 (t, *J* = 7.1 Hz, 3H, 1-OCH$_2$*CH*$_3$/1'-OCH$_2$*CH*$_3$), 0.87 (t, *J* = 7.1 Hz, 3H, 1-OCH$_2$*CH*$_3$/1'-OCH$_2$*CH*$_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 170.0 (s, C-1), 169.0 (s, C-1'), 148.9 (s, C-18/C-19), 148.5 (s, C-18/C-19), 147.2 (s, C-8/C-13), 140.8 (s, C-4), 137.8 (s, C-8/C-13/C-14), 137.5 (s, C-8/C-13/C-14), 130.2 (s, C-16), 129.8 (d, C-15), 129.6 (d, C-5/C-6), 129.1 (d, C-10), 128.2 (d, C-5/C-6), 127.3 (d, C-7), 126.9 (d, C-11), 125.7 (d, C-9), 124.4 (d, C-12), 121.1 (d, C-21), 111.7 (d, C-20), 111.3 (d, C-17), 71.0 (s, C-2), 62.1 (t, 1-O*CH*$_2$CH$_3$/1'-O*CH*$_2$CH$_3$), 61.1 (t, 1-O*CH*$_2$CH$_3$/1'-O*CH*$_2$CH$_3$), 56.1 (q, 18-OCH$_3$/19-OCH$_3$), 56.03 (q, 18-OCH$_3$/19-OCH$_3$), 55.97 (d, C-3), 14.2 (q, 1-OCH$_2$*CH*$_3$/1'-OCH$_2$*CH*$_3$), 13.6 (q, 1-OCH$_2$*CH*$_3$/ 1'-OCH$_2$*CH*$_3$).

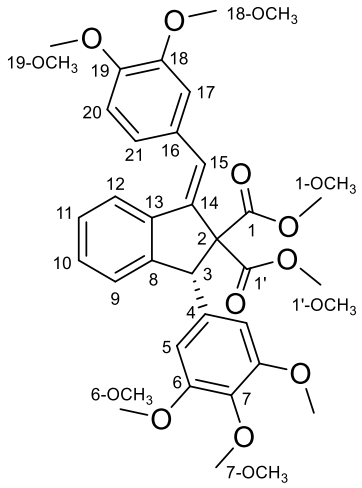
Dimethyl 1-((3,4-dimethoxyphenyl)(hydroxy)methyl)-3-(3,4,5-trimethoxyphenyl)--1,3-dihydro-2*H*-indene-2,2-dicarboxylate (27c):



A solution of **4b** (125 mg, 0.393 mmol) in THF (8 mL) was cooled to −78 °C. *tert*-Butyllithium (231 µL, 0.393 mmol, 1.7 M) was added. After 15 min, a solution of CuBr·DMS (13 mg, 0.063 mmol) and LiBr (60 mg, 0.181 mmol) in THF (3 mL) was added and the mixture was stirred for 5 min. A solution of **8b** (95 mg, 0.306 mmol) in THF (3 mL) was added dropwise. The reaction was warmed to 0 °C over 2 h and ferrocenium hexafluorophosphate (300 mg, 0.906 mmol) was added. After 1 h, the reaction was quenched by saturated NH_4Cl solution (15 mL). The solution was extracted with diethyl ether (3 x 100 mL) and the organic extract was washed with 10% $Na_2S_2O_3$ solution (50 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated and purification by column chromatography (SiO_2, gradient hexane/EA 7:1 to pure EA) afforded 5% of **17d**, 4% of **27c** and 37% of **28c**; $\mathbf{R_f}$ = 0.11 (3:1, hexane/EA); **IR ν [cm^{-1}]:** 2999 (w), 2932 (w), 2838 (w), 1736 (m), 1707 (m), 1591 (m), 1509 (m), 1460 (m), 1423 (m), 1332 (s), 1263 (s), 1239 (s), 1126 (vs), 1026 (m), 767 (w), 736 (w); **MS ESI+ m/z, (%):** 1155 (68, $[2M+Na]^+$), 1123 (48, $[2M+Na-MeOH]^+$), 589 (100, $[M+Na]^+$), 557 (39, $[M+Na-MeOH]^+$); **HRMS ESI+ m/z:** $[M+Na]^+$ Calcd. for $C_{31}H_{34}O_{10}Na$: 589.2044; Found: 589.2049; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.16-7.11 (m, 3H, CH-10, CH-17, CH-20), 7.05 (t, *J* = 7.5 Hz, 1H, CH-11), 6.96-6.91 (m, 2H, CH-12, CH-21), 6.63 (s, 2H, CH-5), 6.59 (d, *J* = 7.7 Hz, 1H, CH-9), 5.08 (s, 1H, CH-3), 4.98 (br t, *J* = 9.6 Hz, 1H, CH-15), 4.41 (d, *J* = 9.6 Hz, 1H, CH-14), 4.27 (br d, *J* = 9.8 Hz, 1H, 15-OH), 3.97 (s, 3H, 1-OCH_3/1‘-OCH_3), 3.94 (s, 6H, 18-OCH_3, 19-OCH_3), 3.88 (s, 3H, 7-OCH_3), 3.82 (s, 6H, 6-OCH_3), 3.39 (s, 3H, 1-OCH_3/1‘-OCH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 175.2 (s, C-1/C-1‘), 168.6 (s, C-1/C-1‘), 152.6 (s, C-6), 149.5 (C-18/C-19), 149.1 (s, C-18/C-19), 142.8 (s, C-8), 141.6 (s, C-13), 137.6 (s, C-7), 137.0 (s, C-16), 134.0 (s, C-4), 127.6 (d, C-11), 127.4 (d, C-10), 125.0 (d, C-12), 123.9 (d, C-9), 119.9 (d, C-21), 111.5 (d, C-20), 111.1 (d, C-17), 108.5 (d, C-5), 74.9 (d, C-15), 70.9 (s, C-2), 61.0 (q, 7-OCH_3), 57.1 (d, C-14), 57.0 (d, C-3), 56.3 (q, 6-OCH_3), 56.11

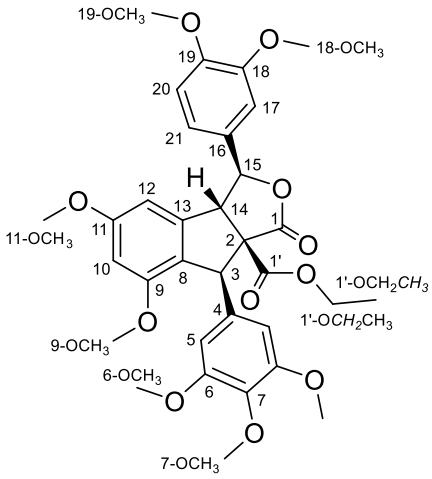
(q, 18-OCH_3/19-OCH_3), 56.09 (q, 18-OCH_3/19-OCH_3), 53.6 (q, 1-OCH_3/1‘-OCH_3), 52.4 (q, 1-OCH_3/1‘-OCH_3).

Dimethyl (*R*,E*)-1-(3,4-dimethoxybenzylidene)-3-(3,4,5-trimethoxyphenyl)-1,3--dihydro-2*H*-indene-2,2-dicarboxylate (28c):



The compound **28c** was prepared in 37% yield according to the procedure for synthesis of compound **27c**, which is described above; $\mathbf{R_f}$ = 0.16 (3:1, hexane/EA); **M.p.** = 155-157 °C; **IR ν [cm^{-1}]:** 2999 (w), 2950 (w), 2837 (w), 1731 (s), 1589 (m), 1509 (s), 1457 (m), 1422 (m), 1330 (m), 1231 (vs), 1123 (vs), 1096 (s), 1025 (s), 1007 (m), 919 (w), 780 (m), 761 (m), 732 (m); **MS ESI+ m/z, (%):** 1119 (5, $[2M+Na]^+$), 571 (100, $[M+Na]^+$); **HRMS ESI+ m/z:** $[M+Na]^+$ Calcd. for $C_{31}H_{32}O_9Na$: 571.1939; Found: 571.1938; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.30 (d, *J* = 7.9 Hz, 1H, CH-12), 7.16 (t, *J* = 7.4 Hz, 1H, CH-10), 7.10 (d, *J* = 7.9 Hz, 1H, CH-9), 7.09 (s, 1H, CH-15), 7.02-6.99 (m, 2H, CH-11, CH-21), 6.96 (d, *J* = 1.9 Hz, 1H, CH-17), 6.89 (d, *J* = 8.2 Hz, CH-20), 6.36 (s, 2H, CH-5), 5.33 (s, 1H, CH-3), 3.93 (s, 3H, 18-OCH_3/19-OCH_3), 3.84 (s, 3H, 18-OCH_3/19-OCH_3), 3.82 (s, 3H, 1-OCH_3/1‘-OCH_3), 3.81 (s, 3H, 7-OCH_3), 3.77 (s, 6H, 6-OCH_3), 3.27 (s, 3H, 1-OCH_3/1‘-OCH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 170.5 (s, C-1/C-1‘), 169.5 (s, C-1/C-1‘), 152.9 (s, C-6), 149.0 (s, C-18/C-19), 148.6 (s, C-18/C-19), 146.6 (s, C-8), 137.8 (s, C-13), 137.4 (s, C-7/C-14), 137.3 (s, C-7/C-14), 136.0 (s, C-4), 130.0 (s, C-16), 129.4 (d, C-15), 129.1 (d, C-10), 127.1 (d, C-11), 125.7 (d, C-9), 124.5 (d, C-12), 121.1 (d, C-21), 111.6 (d, C-20), 111.3 (d, C-17), 106.6 (d, C-5), 71.5 (s, C-2), 61.0 (q, 7-OCH_3), 56.4 (q, 18-OCH_3/19-OCH_3), 56.2 (q, 6-OCH_3), 56.1 (q, 18-OCH_3/19-OCH_3), 56.0 (d, C-3), 53.5 (q, 1-OCH_3/1‘-OCH_3), 52.2 (q, 1-OCH_3/1‘-OCH_3). The relative configuration was determined by X-ray crystallographic analysis available in **Chapter 3.3**.

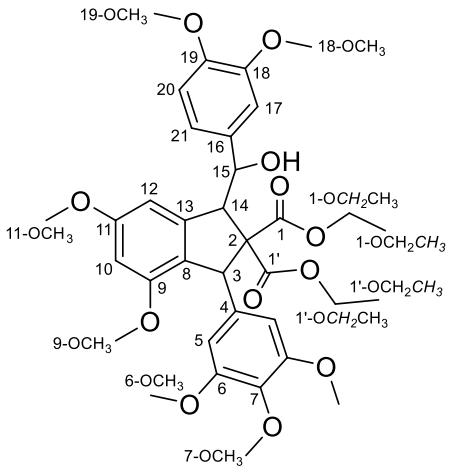
Ethyl (3S*,3aS*,8S*,8aR*)-3-(3,4-dimethoxyphenyl)-5,7-dimethoxy-1-oxo-8-(3,4,5--trimethoxyphenyl)-3a,8-dihydro-1*H*-indeno[1,2-c]furan-8a(3*H*)-carboxylate (26d):



A solution of **4c** (112 mg, 0.296 mmol) in THF (7 mL) was cooled to −78 °C and *tert*-butyllithium (175 µL, 0.296 mmol) was added. After 5 min, a solution of CuBr·DMS (5 mg, 0.024 mmol) and LiBr (13 mg, 0.150 mmol) in THF (3 mL) was added and the solution was stirred for 5 min. Compound **8c** (40 mg, 0.115 mmol) was added and the reaction was warmed to −40 °C over 2 h. Ferrocenium hexafluorophosphate (150 mg, 0.448 mmol) was added and the mixture was warmed to 0 °C. After 2 h, the reaction was quenched by saturated NH_4Cl solution (15 mL). The solution was transferred to the separatory funnel and extracted with diethyl ether (3 x 100 mL). The organic extract was washed with 10% $Na_2S_2O_3$ and the organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and purification by column chromatography (SiO_2, gradient hexane/EA 7:1 to pure EA) gave 75% of **26d** and 54% of **27d**; $\mathbf{R_f}$ = 0.28 (1:1, hexane/EA); **M.p.** = 163-165 °C; **IR ν [cm^{-1}]:** 2938 (w), 2838 (w), 1780 (m), 1735 (w), 1593 (m), 1516 (m), 1461 (m), 1422 (m), 1329 (m), 1259 (m), 1234 (s), 1208 (m), 1151 (s), 1124 (vs), 1068 (m), 1025 (s), 857 (w), 810 (w), 734(w); **MS ESI+ m/z, (%)**: 1239 (6, $[2M+Na]^+$), 647 (14, $[M+K]^+$), 631 (100, $[M+Na]^+$); **HRMS ESI+ m/z:** $[M+Na]^+$ Calcd. for $C_{33}H_{36}O_{11}Na$: 631.2150; Found: 631.2154; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 6.93 (d, *J* = 8.3 Hz, 1H, CH-21), 6.86 (d, *J* = 8.4 Hz, 1H, CH-20), 6.83 (d, *J* = 2.0 Hz, 1H, CH-17), 6.61 (d, *J* = 1.4 Hz, 1H, CH-12), 6.38 (d, *J* = 1.7 Hz, 1H, CH-10), 6.19 (br s, 2H, CH-5), 5.70 (s, 1H, CH-15), 5.04 (s, 1H, CH-3), 4.62 (s, 1H, CH-14), 3.89 (s, 3H, 11-OCH_3), 3.88 (s, 3H, 18-OCH_3), 3.87 (s, 3H, 19-OCH_3), 3.75 (s, 3H, 7-OCH_3), 3.72 (s, 6H, 6-OCH_3), 3.66 (s, 3H, 9-OCH_3), 3.55 (q, *J* = 7.2 Hz, 2H, 1'-O*CH*$_2$$CH_3$), 0.71 (t, *J* = 7.1 Hz, 3H, 1'-OCH_2*CH*$_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 174.8 (s, C-1), 166.2 (s, C-1'), 162.6 (s, C-11), 157.1 (s, C-9), 152.9 (s, C-6), 149. 4 (s, C-18/C-19), 149.1 (s, C-18/C-19), 143.4 (s, C-13), 137.3 (s, C-7), 134.9 (s, C-4), 131.5 (s, C-16), 123.1 (s, C-8), 117.4 (d, C-21), 111.3 (d, C-20), 108.1 (d, C-17), 105.9 (d, C-5), 99.5 (d, C-12), 99.0 (d, C-10), 84.4 (d, C-15), 66.6 (s, C-2), 61.9 (t, 1'-O*CH*$_2$$CH_3$), 60.9 (q, 7-$OCH_3$),

56.48 (d, C-14), 56.46 (d, C-3), 56.3 (q, 6-OCH_3), 56.2 (q, 11-OCH_3/18-OCH_3/19-OCH_3), 56.1 (q, 11-OCH_3/18-OCH_3/19-OCH_3), 55.9 (q, 11-OCH_3/18-OCH_3/19-OCH_3), 55.6 (q, 9-OCH_3), 13.6 (q, 1'-OCH_2CH_3). The relative configuration was determined by NOE experiment and X-ray crystallographic analysis available in **Chapter 3.3**.

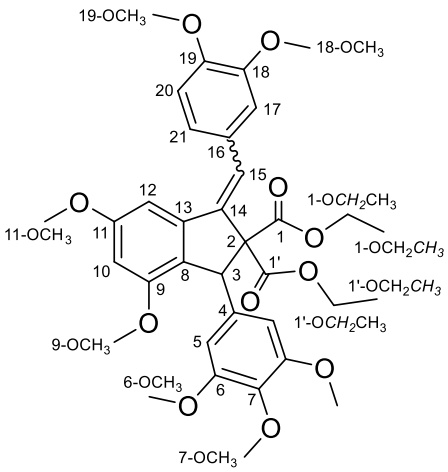
Diethyl 1-((3,4-dimethoxyphenyl)(hydroxy)methyl)-4,6-dimethoxy-3-(3,4,5--trimethoxyphenyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (27d):



The compound **27d** with the highest yield was prepared according to the procedure for synthesis of compound **26d** except for diisopropylamine (10 µL, 0.071 mmol), which was added to the reaction mixture after ferrocenium salt at −40 °C and warmed to 0 °C. After workup, the reaction yielded 17% of **26d**, 54% of **27d** and 15% of **28d**. The compound **27d** spontaneously lactonizes into **26d** in solution; $\mathbf{R_f}$ = 0.17 (1:1, hexane/EA); **IR ν [cm^{-1}]:** 2937 (w), 2837 (w), 1782 (m), 1727 (m), 1592 (m), 1514 (m), 1458 (m), 1421 (m), 1329 (m), 1258 (s), 1234 (s), 1200 (m), 1148 (s), 1123 (vs), 1069 (m), 1023 (s), 857 (m), 806 (m), 732 (m); **MS ESI+ m/z, (%)**: 1285 (12, $[2M+Na-CH_2CH_3OH]^+$), 1239 (12, $[2M+Na-2CH_2CH_3OH]^+$), 677 (47, $[M+Na]^+$), 637 (100, $[M+H-H_2O]^+$), 625 (92, $[M+H-CH_2CH_3]^+$), 609 (19, $[M-CH_2CH_3OH]^+$); **HRMS ESI+ m/z,** $[M+Na]^+$: Calcd. for $C_{35}H_{42}O_{12}Na$: 677.2569; Found: 677.2559; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 6.95-6.85 (m, 3H, CH-17, CH-20, CH-21), 6.25 (s, 2H, CH-5), 6.24 (d, *J* = 2.0 Hz, 1H, CH-10), 5.78 (d, J = 1.7 Hz, 1H, CH-12), 4.97 (s, 1H, CH-3), 4.75 (d, *J* = 8.8 Hz, 1H, CH-15), 4.68 (d, *J* = 8.8 Hz, 1H, CH-14), 4.34-4.15 (m, 2H, 1-O*CH*$_2$CH$_3$/1'-O*CH*$_2$CH$_3$), 3.83 (s, 6H, 18-OCH_3, 19-OCH_3), 3.79 (s, 3H, 7-OCH_3), 3.73 (s, 6H, 6-OCH_3), 3.72-3.58 (m, 2H, 1-O*CH*$_2$CH$_3$/1'-O*CH*$_2$CH$_3$) 3.57 (s, 3H, 11-OCH_3), 3.54 (s, 3H, 9-OCH_3), 2.04 (s, 1H, 15-OH), 1.27 (t, *J* = 6.7 Hz, 3H, 1-OCH_2*CH*$_3$/1'-OCH_2*CH*$_3$), 0.93 (t, *J* = 7.0 Hz, 3H, 1-OCH_2*CH*$_3$/ 1'-OCH_2*CH*$_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 171.1 (s, C-1/C-1'), 170.7 (s, C-1/C-1'), 160.8 (s, C-9), 156.2 (s, C-11), 152.6 (s, C-6), 149.2 (s, C-18/C-19). 149.1 (C-18/C-19), 142.7 (s, C-13), 136.8 (s, C-7), 135.8 (s, C-4), 135.3 (s, C-16), 124.1 (s, C-8), 120.4 (d, C-21), 111.0 (d, C-20), 110.8 (d, C-17), 106.0 (d, C-5), 101.4 (d, CH-12), 98.5 (d, C-10), 75.0

(d, C-15), 70.5 (s, C-2), 62.0 (t, 1-O*CH*$_2$CH$_3$/1‘-O*CH*$_2$CH$_3$), 61.6 (t, 1-O*CH*$_2$CH$_3$/1‘-O*CH*$_2$CH$_3$), 60.9 (q, 7-OCH$_3$), 57.1 (d, C-14), 56.2 (q, 5-OCH$_3$), 55.93 (q, 18-OCH$_3$/19-OCH$_3$), 55.91 (q, 18-OCH$_3$/19-OCH$_3$), 55.5 (q, 9-OCH$_3$/11-OCH$_3$), 55.3 (9-OCH$_3$/11-OCH$_3$), 54.1 (d, C-3), 14.1 (q, 1-OCH$_2$*CH$_3$*/1‘-OCH$_2$*CH$_3$*), 13.7 (q, 1-OCH$_2$*CH$_3$*/1‘-O*CH*$_2$CH$_3$).

Diethyl 1-(3,4-dimethoxybenzylidene)-4,6-dimethoxy-3-(3,4,5-trimethoxyphenyl)--1,3-dihydro-2*H*-indene-2,2-dicarboxylate (28d):



The compound **28d** with the highest yield was prepared according to the procedure for synthesis of compound **26d** except for temperature conditions for oxidation. Ferrocenium hexafluorophosphate (150 mg, 0.448 mmol) was added at −10 °C, the reaction mixture was warmed to r.t and quenched after 1.5 h. After work up the reaction gave 34 % of **26d**, 19% of **27d** and 18% of **28d**; **R$_f$** = 0.43 (1:1, hexane/EA); **IR ν [cm^{-1}]:** 2999 (w), 2935 (w), 2836 (w), 1733 (w), 1594 (m), 1512 (s), 1455 (m), 1420 (m), 1326 (m), 1262 (s), 1232 (s), 1200 (s), 1154 (s), 1138 (s), 1074 (m), 1025 (m), 964 (w), 829 (w), 807 (w), 734 (w)**; MS ESI+ m/z, (%)**: 1295 (45, [2M+Na]$^+$), 659 (100, [M+Na]$^+$), 631 (6, [M+Na−CH$_2$CH$_4$]$^+$); **HRMS ESI+ m/z,** [M+Na]$^+$: Calcd.: 659.2463, found: 659.2457; **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.14 (s, 1H, CH-15), 7.03 (d, *J* = 8.2 Hz, 1H, CH-21), 6.98 (d, *J* = 1.7 Hz, 1H, CH-17), 6.89 (d, *J* = 8.2 Hz, 1H, CH-20) 6.41 (s, 2H, CH-5), 6.39 (d, *J* = 2.1 Hz, 1H, CH-10/CH-12), 6.25 (d, *J* = 2.0 Hz, 1H, CH-10/CH-12), 5.10 (s, 1H, CH-3), 4.30-4.17 (m, 2H, 1-O*CH*$_2$CH$_3$/1’-O*CH*$_2$CH$_3$), 3.92 (s, 3H, 18-OCH$_3$), 3.85 (s, 3H, 19-OCH$_3$), 3.78 (s, 3H, 7-OCH$_3$), 3.77 (s, 6H, 6-OCH$_3$), 3.75-3.69 (m, 2H, 1-O*CH*$_2$CH$_3$/1’-O*CH*$_2$CH$_3$), 3.65 (s, 3H, 9-OCH$_3$), 3.49 (s, 3H, 11-OCH$_3$), 1.26 (t, *J* = 7.1 Hz, 3H, 1-OCH$_2$*CH$_3$*/1’-OCH$_2$*CH$_3$*), 0.93 (t, *J* = 7.1 Hz, 3H, 1-OCH$_2$*CH$_3$*/1’-OCH$_2$*CH$_3$*); **^{13}C NMR (100 MHz, CDCl$_3$):** δ = 169.8 (s, C-1/C-1’), 168.7 (s, C-1/C-1’), 160.4 (s, C-11), 156.6 (s, C-9), 152.5 (s, C-6), 148.9 (s, C-19), 148.6 (s, C-18), 139.2 (s, C-13), 137.3 (s, C-7), 136.0 (s, C-4), 130.6 (d, C-15), 130.2 (s, C-16), 128.4 (s, C-8), 121.4 (d, C-21), 113.3 (s, C-14), 111.9 (d, C-20), 111.2 (d, C-17), 106.4 (d, C-5), 105.1 (s, C-12), 100.0 (d, C-10/C-2), 99.9 (d, C-10), 71.0 (s, C-2), 62.1

(t, 1-O*CH*$_2$CH$_3$/1'-O*CH*$_2$CH$_3$), 61.1 (t, 1-O*CH*$_2$CH$_3$/1'-O*CH*$_2$CH$_3$), 61.0 (q, 7-OCH$_3$), 56.13 (q, 18-OCH$_3$), 56.12 (q, 6-OCH$_3$), 56.0 (q, 19-OCH$_3$), 55.6 (q, 9-OCH$_3$), 55.3 (q, 11-OCH$_3$), 53.1 (d, C-3), 14.2 (q, 1-OCH$_2$*CH$_3$*/1'-OCH$_2$*CH$_3$*), 13.8 (q, 1-OCH$_2$*CH$_3$*/1'-OCH$_2$*CH$_3$*).

5.3 Crystallographic data

Crystallographic data for **28c** and **26d** were collected on Bruker D8 VENTURE Kappa Duo PHOTON100 by IμS micro-focus sealed tube CuKα (λ = 1.54178 Å). The measurements were performed at low temperature 120K using CryostreamCooler800. The multi-scan absorption corrections were carried on for both crystals. The structures were solved by direct methods (XT[73]) and refined by full matrix least squares based on F^2 (SHELXL2014[74]). The hydrogen atoms on carbon were fixed into idealised positions (riding model) and assigned temperature factors either $H_{iso}(H) = 1.2\ U_{eq}$(pivot atom) or $H_{iso}(H) = 1.5\ U_{eq}$ (pivot atom) for methyl moiety.

The crystal of **26d** contains disordered ethyl acetate solvent in the unit cell. To improve precision of principal molecule the SQUEEZE procedure within PLATON[75] was applied to remove the contribution of solvent to diffraction data.

Table 5.1 Crystal data, data collection and refinement parameters for **28c** and **26d**.

Compound		**28c**	**26d**
Chemical formula		$C_{31}H_{32}O_9$	$C_{35}H_{40}O_{12}$
M_r		548.56	652.67
Crystal habit		Prism, colourless	Prism, colourless
Crystal size [mm]		0.35 × 0.30 × 0.22	0.33 × 0.25 × 0.19
Crystal system		Monoclinic	Triclinic
Space group		$P2_1/c$	$P\bar{1}$
Temperature [K]		120	120
Unit cell dimensions	a, b, c [Å]	17.8164 (13), 11.3656 (8), 14.4031 (11)	7.9688 (5), 14.5204 (8), 14.7413 (8)
	α [°]		68.271 (2)
	β [°]	109.524 (3)	86.125 (2)
	γ [°]		88.431 (2)
Volume [Å^3]		2748.8 (4)	1580.89 (16)
Z		4	2
Radiation type		Cu $K\alpha$	Cu $K\alpha$
D_x [Mg m^{-3}]		1.326	1.371
μ [mm^{-1}]		0.81	0.86
θ_{max}, θ_{min} [°]		72.4, 2.6	77.7, 3.2
Diffractometer		Bruker D8 VENTURE Kappa Duo PHOTON 100 CMOS	
Absorption correction		Multi-scan, *SADABS2016*/2 - Bruker AXS area detector scaling and absorption correction	
T_{min}, T_{max}		0.78, 0.85	0.55, 0.85
Measured reflections		28395	43257
Independent reflections		5392	6665
Observed reflections [$I > 2\sigma(I)$]		4867	6191
R_{int}		0.036	0.030
$(\sin\theta/\lambda)_{max}$ [Å^{-1}]		0.618	0.634
R [$F^2 > 2\sigma(F^2)$], wR [F^2], S		0.034, 0.087, 1.05	0.036, 0.097, 1.04
Reflections refined		5392	6665
Parameters refined		368	405
H-atom treatment		H-atom parameters constrained	
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ [e Å^{-3}]		0.29, −0.22	0.35, −0.21

6 REFERENCES

1. Sahai, M.; Gössinger, E.; Luzhetska, M.; Härle, J.; Begum, S. A.; Ray, A. B. *Progress in the Chemistry of Organic Natural Products*; Kinghorn, A. D.; Falk, H.; Kobayashi, J., Eds.; Springer-Verlag: Wien, **2010**; Vol. 93.
2. Chong, J.; Poutaraud, A.; Hugueney, P. *Plant Sci.* **2009**, *177*, 143.
3. Dixon, R. A.; Paiva, N. L. *Plant Cell* **1995**, *7*, 1085.
4. Baur, J. A.; Sinclair, D. A. *Nat. Rev. Drug Discov.* **2006**, *5*, 493.
5. Roupe, K. A.; Remsberg, C. M.; Yáñez, J. A.; Davies, N. M. *Curr. Clin. Pharmacol.* **2006**, *1*, 81.
6. Snyder, S. A.; Zografos, A. L.; Lin, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 8186.
7. Szewczuk, L. M.; Forti, L.; Stivala, L. A.; Penning, T. M. *J. Biol. Chem.* **2004**, *279*, 22727.
8. Ohguchi, K.; Tanaka, T.; Ito, T.; Iinuma, M.; Matsumoto, K.; Akao, Y.; Nozawa, Y. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 1587.
9. Young, R. J.; Lovell, P. A. *Introduction to Polymers: Third Edition*; CRC Press, **2011**.
10. Shen, T.; Wang, X.-N.; Lou, H.-X. *Nat. Prod. Rep.* **2009**, *26*, 916.
11. Pan, J.-Y.; Chen, S.-L.; Yang, M.-H.; Wu, J.; Sinkkonen, J.; Zou, K. *Nat. Prod. Rep.* **2009**, *26*, 1251.
12. Bertrand Teponno, R.; Kusari, S.; Spiteller, M. *Nat. Prod. Rep.* **2016**, *33*, 1044.
13. Kuo, Y.-H.; Wu, C.-H.; Wu, R.-E.; Lin, S.-T. *Chem. Pharm. Bull. (Tokyo)* **1995**, *43*, 1267.
14. Yao, C.-S.; Lin, M.; Wang, L. *Chem. Pharm. Bull. (Tokyo)* **2006**, *54*, 1053.
15. Lee, D.; Cuendet, M.; Vigo, J. S.; Graham, J. G.; Cabieses, F.; Fong, H. H. S.; Pezzuto, J. M.; Kinghorn, A. D. *Org. Lett.* **2001**, *3*, 2169.
16. Banwell, M. G.; Bezos, A.; Chand, S.; Dannhardt, G.; Kiefer, W.; Nowe, U.; Parish, C. R.; Savage, G. P.; Ulbrich, H. *Org. Biomol. Chem.* **2003**, *1*, 2427.
17. Lam, S.-H.; Chen, J.-M.; Kang, C.-J.; Chen, C.-H.; Lee, S.-S. *Phytochemistry* **2008**, *69*, 1173.
18. Dubrovina, A. S.; Kiselev, K. V. *Planta* **2017**, *246*, 597.
19. Ferrer, J.-L.; M. Jez, J.; E. Bowman, M.; Dixon, R.; Noel, J. *Nat. Struct. Biol.* **1999**, *6*, 775.
20. MacDonald, M. J.; D'Cunha, G. B. *Biochem. Cell Biol.* **2007**, *85*, 273.
21. Yu, O.; Jez, J. M. *Plant J.* **2008**, *54*, 750.
22. Dubrovina, A. S.; Kiselev, K. V. *Planta* **2017**.
23. Austin, M. B.; Noel, J. P. *Nat. Prod. Rep.* **2003**, *20*, 79.

24. Varbanova Herde, M.; Porter, K.; Lu, F.; Ralph, J.; Hammerschmidt, R.; Daniel Jones, A.; Day, B. *Plant Physiol.* **2011**, *157*, 1056.
25. Yang, G.-X.; Hu, C.-Q. *Chin. J. Org. Chem.* **2003**, *23*, 873.
26. Guo, L.; Yang, X.; Sun, X.; Wu, X. *Phytochem. Lett.* **2017**, *20*, 32.
27. Yang, G. X.; Zhou, J. T.; Li, Y. Z.; Hu, C. Q. *Planta Med.* **2005**, *71*, 569.
28. Meng, Q.; Niu, Y.; Niu, X.; Roubin, R. H.; Hanrahan, J. R. *J. Ethnopharmacol.* **2009**, *124*, 350.
29. Lin, M.; Li, J. B.; Wu, B.; Zheng, Q. T. *Phytochemistry* **1991**, *30*, 4201.
30. Lin, M.; Li, J. B.; Li, S. Z.; Yu, D. Q.; Liang, X. T. *Phytochemistry* **1992**, *31*, 633.
31. Ali, Z.; Tanaka, T.; Iliya, I.; Iinuma, M.; Furusawa, M.; Ito, T.; Nakaya, K.; Murata, J.; Darnaedi, D. *J. Nat. Prod.* **2003**, *66*, 558.
32. Kawazoe, K.; Shimogai, N.; Takaishi, Y.; Rao, K. S.; Imakura, Y. *Phytochemistry* **1997**, *44*, 1569.
33. Kulesh, N. I.; Denisenko, V. A.; Maksimov, O. B. *Phytochemistry* **1995**, *40*, 1001.
34. Kobayashi, M.; Mahmud, T.; Yoshioka, N.; Hori, K.; Shibuya, H.; Kitagawa, I. *Chem. Pharm. Bull. (Tokyo)* **1996**, *44*, 2249.
35. Ting, X.; Uno, T.; Ogino, F.; Ai, C.; Duo, J.; Sankawa, U. *Chem. Pharm. Bull. (Tokyo)* **2005**, *53*, 1204.
36. Xiong, Y.; Guo, D.; Huang, H. *Zhongguo Xiandai Zhongyao* **2008**, *10*, 20.
37. Xu, S.; Shang, M.-Y.; Liu, G.-X.; Xu, F.; Wang, X.; Shou, C.-C.; Cai, S.-Q. *Mol. Basel Switz.* **2013**, *18*, 5265.
38. Utkina, N.; I. Kulesh, N. *Pharm. Chem. J.* **2012**, *46*.
39. Kuspradini, H.; Mitsunaga, T.; Ohashi, H. *J. Wood Sci.* **2009**, *55*, 308.
40. Fedoreev, S. A.; Kulish, N. I.; Glebko, L. I.; Pokushalova, T. V.; Veselova, M. V.; Saratikov, A. S.; Vengerovskii, A. I.; Chuchalin, V. S. *Pharm. Chem. J.* **2004**, *38*, 605.
41. Al-Farhan, E.; Keehn, P. M.; Stevenson, R. *J. Chem. Res. S* **1992**, 36.
42. MacMillan, J.; Martin, I. L.; Morris, D. J. *Tetrahedron* **1969**, *25*, 905.
43. Müller, A.; Mészáros, M.; Körmendy, K.; Kucsman, Á. *J. Org. Chem.* **1952**, *17*, 787.
44. Leary, G. *Aust. J. Chem.* **1977**, *30*, 1133.
45. Chiang Hung-Cheh; Li Shyh-Yuan *J. Chin. Chem. Soc.* **2013**, *25*, 141.
46. Salomone, A.; Capriati, V.; Florio, S.; Luisi, R. *Org. Lett.* **2008**, *10*, 1947.
47. Li, W.; Zang, P.; Li, H.; Yang, S. *Prog. Chem.* **2012**, *24*, 545.
48. McMurry, J. *Organická chemie*; Překlady vysokoškolských učebnic; 1.; VUTIUM: Brno, Praha, **2015**.

49. Harcken, C.; Martin, S. F. *Org. Lett.* **2001**, *3*, 3591.
50. Knoevenagel E. *Berichte Dtsch. Chem. Ges.* **2006**, *31*, 2596.
51. Chung, S. K.; Dunn, L. B., Jr. *J. Org. Chem.* **1983**, *48*, 1125.
52. Jahn, U.; Hartmann, P. *Chem. Commun.* **1998**, 209.
53. Jahn, U.; Hartmann, P. *J. Chem. Soc. [Perkin 1]* **2001**, *0*, 2277.
54. Babu, B. H.; Prasad, G. S.; Raju, C. N.; Rao, M. V. B. *Curr. Org. Synth.* **2017**, *14*, 883.
55. Byrne, P. A.; Gilheany, D. G. *Chem. Soc. Rev.* **2013**, *42*, 6670.
56. Braun, M. Modern Enolate Chemistry: From Preparation to Applications in Asymmetric Synthesis; Wiley, **2015**.
57. Alexakis, A.; Krause, N.; Woodward, S. *Copper-Catalyzed Asymmetric Synthesis*; Wiley, **2014**.
58. Cahiez, G.; Venegas, P.; Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Chem. Soc. Chem. Commun.* **1992**, *0*, 1406.
59. Wietelmann, U.; Klett, J. *Z. Anorg. Allg. Chem.* **2018**, *644*, 194.
60. Gutmann, V. *Coord. Chem. Rev.* **1976**, *18*, 225.
61. Poon, P.; K. Banerjee, A.; Laya, M. *J. Chem. Res.* **2011**, *35*.
62. Bailey, W.; Rathman, T. **2007**; pp 205.
63. Haynes Richard K.; Vonwiller Simone C.; Luderer Matthew R. *Encycl. Reag. Org. Synth.* **2006**.
64. Dykstra Robert R. *Encycl. Reag. Org. Synth.* **2001**.
65. de Bolster M. W. G.; Groeneveld W. L. *Recl. Trav. Chim. Pays-Bas* **2010**, *90*, 477.
66. Webb, R. J.; Lowery, M. D.; Shiomi, Y.; Sorai, M.; Wittebort, R. J.; Hendrickson, D. N. *Inorg. Chem.* **1992**, *31*, 5211.
67. Jahn, U. *Chem. Commun.* **2001**, *0*, 1600.
68. Lin, C.-K.; Prabhakar, C.; Yang, J.-S. *J. Phys. Chem. A* **2011**, *115*, 3233.
69. Yu, J.; Li, N.; Chen, D.-F.; Luo, S.-W. *Tetrahedron Lett.* **2014**, *55*, 2859.
70. Liao, Y.-R.; Kuo, P.-C.; Huang, S.-C.; Liang, J.-W.; Wu, T.-S. *Tetrahedron Lett.* **2012**, *53*, 6202.
71. Zhang, S.; Cheng, K.; Wang, X.; Yin, H. *Bioorg. Med. Chem.* **2012**, *20*, 6073.
72. Gu, J.-X.; Holland, H. L. *Synth. Commun.* **1998**, *28*, 3305.
73. Sheldrick, G. M. Acta Crystallogr. Sect. Found. Adv. **2015**, 71, 3.
74. Sheldrick, G. M. Acta Crystallogr. Sect. C Struct. Chem. **2015**, 71, 3.
75. Spek, A. L. Acta Crystallogr. D Biol. Crystallogr. **2009**, 65, 148.